

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**208716Orig1s000**

**OTHER REVIEW(S)**

## Clinical Inspection Summary

|                                   |                                                                                                                                                                                                              |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                       | September 26, 2017                                                                                                                                                                                           |
| <b>From</b>                       | Sharon Gershon, Pharm.D, Reviewer<br>Susan Thompson, M.D., Team Leader,<br>Kassa Ayalew, M.D., M.P.H., Branch Chief,<br>OSI /DCCE/GCPAB                                                                      |
| <b>To</b>                         | Lynn Howie, M.D, Clinical Reviewer<br>Laleh Amiri-Kordestani, M.D, Clinical Team Leader<br>Julia Beaver, M.D, Division Director<br>Janice Kim, Regulatory Project Manager<br>Division of Oncology Products 1 |
| <b>NDA #</b>                      | NDA 208716                                                                                                                                                                                                   |
| <b>Applicant</b>                  | Eli Lilly and Company                                                                                                                                                                                        |
| <b>Drug</b>                       | Verzenio® (abemaciclib)                                                                                                                                                                                      |
| <b>NME</b>                        | Yes                                                                                                                                                                                                          |
| <b>Therapeutic Classification</b> | Cyclin-dependent kinase inhibitor                                                                                                                                                                            |
| <b>Proposed Indication</b>        | Treatment of patients with advanced or metastatic breast cancer                                                                                                                                              |
| <b>Consultation Request Date</b>  | May 26, 2017                                                                                                                                                                                                 |
| <b>Summary Goal Date</b>          | September 26, 2017                                                                                                                                                                                           |
| <b>Action Goal Date</b>           | September 29, 2017                                                                                                                                                                                           |
| <b>PDUFA Date</b>                 | January 5, 2018                                                                                                                                                                                              |

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The data from Studies I3Y-MC-JPBL and I3Y-MC-JPBN were submitted to the Agency in support of NDA 208716. A total of six clinical sites were selected for audit - three domestic sites and three foreign sites. The domestic sites were Peter Kaufman (New Hampshire, Site 104 for JPBL), Sara Tolaney (Massachusetts, Site 132 for JPBN and Site 400 for JPBL), and Maura Dickler (New York, Site 100 for JPBL and Site 114 for JPBN). The foreign sites were Dr. Claudia Arce Salinas (Mexico, Site 280 for JPBL), Dr. Hiroji Iwata (Japan, Site 708 for JPBL) and Dr. Sung-Bae Kim (S. Korea, Site 805 for JPBL).

The primary efficacy endpoint, Progression-Free Survival (PFS), and tumor size measurements were verified with the source records generated at the inspected clinical sites.

There were no significant inspectional findings for clinical investigators Dr. Peter Kaufman, Dr. Sara Tolaney, Dr. Hiroji Iwata, and Dr. Sung-Bae Kim. Minor violations were found during the inspection of Dr. Maura Dickler and the inspection was classified as VAI. Those violations are unlikely to impact the outcome of the study or the reliability of the data. At the Arce Salinas site, discrepancies were found between image scans and source documents and data listings with respect to tumor location or identity, tumor size measurements, and radiology scan date for seven of the eleven subjects, which ultimately impacted the RECIST assessment

for disease progression for three subjects. Two subjects had better results than what the data listings showed and one had worse results. The clinical investigator provided corrected values in a letter and agreed to re-enter this data into the eCRF by October 15, 2017. Since datalock has occurred, OSI recommends conducting a sensitivity analysis, to determine its impact on the overall efficacy analysis.

. In general, the studies were conducted adequately to support approval.

## II. BACKGROUND

Eli Lilly and Company (Lilly) seeks approval to market abemaciclib in combination with fulvestrant to treat women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer or metastatic breast cancer whose disease has progressed after hormonal therapy and prior chemotherapy. The pivotal trials to support efficacy for this application were I3Y-MC-JPBL (MONARCH 2) and I3Y-MC-JPBN (MONARCH 1).

| Protocol Number | Study ID<br>(Study Title)                                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I3Y-MC-JPBL     | A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Fulvestrant with or w/o Abemaciclib for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer |
| I3Y-MC-JPBN     | A Phase 2 Study of LY2835219 for Patients with Previously Treated Hormone Receptor Positive, HER2 Negative Metastatic Breast Cancer                                                                      |

**Study 13Y-MC-JPBL (MONARCH 2)** was a global, multicenter, double-blind, placebo-controlled, Phase 3 trial for women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer who had disease progression following endocrine therapy randomized to receive fulvestrant with or without abemaciclib.

Number of Subjects: 446 subjects to active drug and 223 subjects to placebo.

Number of Sites: 145 study centers in 19 countries, including the U.S.

Date of first patient enrolled: August 7, 2014

Data cutoff date: February 14, 2017

Primary objective: to compare abemaciclib plus fulvestrant (A+F) versus placebo plus fulvestrant (P+F) with respect to progression-free survival (PFS) for women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer.

Efficacy: The primary efficacy endpoint was to compare A+F versus P+F with respect to investigator-assessed PFS as defined by RECIST version 1.1 for women with HR+, HER2- advanced or metastatic breast cancer.

Secondary efficacy endpoints were to compare A+F versus P+F with respect to Overall Survival (OS); OS rate at 1, 2, and 3 years; objective response rate (ORR; complete response [CR] + partial response [PR]); duration of response (DoR; CR+ PR); disease control rate (DCR; CR + PR + stable disease [SD]) and clinical benefit rate (CBR; CR + PR + SD  $\geq$  6 months).

**Study I3Y-MC-JPBN (MONARCH 1)** was a multicenter, single-arm, open-label study to evaluate the antitumor activity of abemaciclib in patients with HR+, HER2- mBC whose disease progressed after endocrine therapy and who received 1 or 2 prior chemotherapy regimens in the metastatic setting.

Number of Subjects: 132 subjects randomized who received at least one dose of study drug.  
Number of Sites: 35 study centers in 4 countries, including the U.S.

Date of first patient enrolled: June 10, 2014

Data cutoff date: April 30, 2016

Primary Objective: to evaluate abemaciclib with respect to objective response rate (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 hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (mBC).

Primary Efficacy: ORR by investigator assessment as defined by RECIST version 1.1. The final efficacy analysis of the primary endpoint occurred 12 months after the last patient had entered treatment.

Secondary efficacy endpoints: DoR, DCR, CBR, PFS, and OS. ORR, DoR, DCR, CBR, and PFS were assessed by both investigator and independent review.

#### **Objectives of Inspections:**

- a. Verify primary efficacy endpoint of PFS as determined by the clinical investigator for all enrolled subjects.
- b. Verify tumor measurements and tumor response assessments according to RECIST.
- c. Verify key secondary efficacy endpoints for a sample of enrolled subjects:
  - Change in tumor size from baseline to best overall response
  - Overall survival (OS)
- d. Identification, documentation, and reporting of AEs for a sample of enrolled subjects.
- e. General compliance with the investigational plan.

#### **Reasons for Site Selection:**

Dr. Kaufman was a moderate- range enroller, had relatively high site efficacy compared to other study sites, and has conducted many IND studies.

Dr. Arce Salinas was a moderate-range enroller, had high site efficacy results, and reported a low number of protocol violations.

Dr. Iwata was a moderate-range enroller, had high site efficacy results, a low number of serious adverse events (SAEs), low number of deaths, low number of protocol violations, and contributes to the low death rates in the Asia/Pacific compared to other regions.

Dr. Sung-Bae Kim was a moderate enroller, and had high site-weighted efficacy.

Dr. Tolaney had high enrollment in the JPBN study and conducted both studies.

Dr. Dickler had high enrollment in the JPBN study, and had high site efficacy results favorable to study drug for the JPBN study. She also conducted both studies.

### III. RESULTS (by site):

| Name of CI, Address                              | Protocol #, Site #, and # of Subjects enrolled | Inspection Dates       | Final Classification |
|--------------------------------------------------|------------------------------------------------|------------------------|----------------------|
| Peter Kaufman<br>Lebanon, NH                     | 13Y-MC-JPBL<br>Site #104<br>13 subjects        | July 17 – 21,<br>2017  | NAI                  |
| Claudia Arce Salinas<br>México, Federal District | 13Y-MC-JPBL<br>Site #280<br>11 subjects        | August 21-<br>25, 2017 | Preliminary<br>VAI   |
| Hiroji Iwata<br>Nagoya, Aichi                    | 13Y-MC-JPBL<br>Site #708<br>11 subjects        | August 14-<br>17, 2017 | NAI                  |
| Sung-Bae Kim<br>Seoul, Korea                     | 13Y-MC-JPBL<br>Site #805<br>11 subjects        | August 21-<br>25, 2017 | NAI                  |

|                                     |                                         |                        |     |
|-------------------------------------|-----------------------------------------|------------------------|-----|
| Sara Tolaney<br>Boston, MA 02215    | 13Y-MC-JPBL<br>Site #132<br>6 subjects  | August 2 –<br>24, 2017 | NAI |
|                                     | 13Y-MC-JPBN<br>Site #400<br>17 subjects |                        |     |
| Maura Dickler<br>New York, NY 10065 | 13Y-MC-JPBN<br>Site #100<br>17 subjects | July 18 – 27,<br>2017  | VAI |
|                                     | 13Y-MC-JPBL<br>Site #114<br>6 subjects  |                        |     |

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Peter Kaufman**  
**1 Medical Center Dr**  
**Breast Oncology**  
**Lebanon, NH 03756-1000**

The inspection reviewed the conduct of clinical study 13Y-MC-JPBL (Monarch 2). Dr. Kaufman was a moderate enroller, had relatively high site efficacy results compared to other study sites, and has conducted many studies under IND s. Dr. Kaufman has 22 IND studies in the COMIS database, and no prior inspections.

The site screened 13 subjects and enrolled 13 subjects. Six subjects had progression of disease, three of which were deaths, and one subject withdrew consent following an adverse event. Three subjects were on active treatment at the time of the inspection. This site was closed to enrollment on November 24, 2015.

The field investigator reviewed all 13 subject records to verify: 1) protocol adherence; 2) inclusion and exclusion criteria were met; 3) randomization; 4) test article accountability; 6) concomitant medications; 7) identification of key personnel involved in study; 8) condition of the subject at time of entry and during study participation; 9) adverse event reporting, and 10) comparing source documentation with the eCRF and

data listings for tumor size measurements, visit dates, tumor response and assessment, and all other data.

All subjects met the inclusion and exclusion criteria. The primary efficacy endpoint Progression-Free Survival (PFS) was verified, and there were no discrepancies. Adverse events did not appear to be under-reported. Laboratory data, concomitant medications, and visit dates were spot-checked. There were no major discrepancies.

The site had a list of approximately 47 protocol deviations which were categorized as minor or major. The major protocol deviations appear to have been submitted to the sponsor, and were reported as protocol deviations within the data listings. Examples are Subject 1385 and Subject 1700 who missed inclusion criteria #10 because prior anti-cancer treatment was stopped late. For the minor deviations that were not reported to the data listings, documentation exists that action was taken at the site in that the staff was counseled on the correct procedure. Examples were laboratory assessments not signed or reviewed late for clinical significance. Minor deviations also concerned tumor measurements. For example, for Subject 104-1637, tumor measurement was documented into the sponsor's electronic records as 7 mm, whereas the radiology report documented the diameter measurement as 8 mm. It is the opinion of this reviewer that as a whole, these protocol deviations do not adversely impact patient safety or data integrity. The site took corrective action to prevent recurrence.

The subject binders were in good condition, well organized and sequential. Source documentation consisted of printed electronic medical records (EMR) visit notes, laboratory or imaging reports, demographic information, and hand-written questionnaires. Documentation was present on exposure of study test article in Interactive Web Response System (IWRS), and on randomization. Subject diaries were collected at most visits, and reasons were noted when a diary was not collected.

The protocol deviations described above have been included in the study report. Although protocol violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The data from Dr. Kaufman's site associated with Study 13Y-MC-JPBL appear reliable.

**2. Claudia Arce Salinas**  
**Avenida San Fernando 22**  
**Colonia Barrio del Niño de Jesús**  
**México, Federal District 14080**

The inspection reviewed the conduct of clinical Study 13Y-MC-JPBL (Monarch 2). Dr. Arce has four IND studies in the COMIS database, and no prior inspections. Dr. Arce was a moderate-range enroller, had high site efficacy results, and reported a low number of protocol violations.

The site screened 13 subjects and enrolled 11 subjects. The study was ongoing at the time of the inspection, with four subjects currently on active treatment. The field

investigator reviewed records for all 13 subjects. The primary endpoint PFS was verifiable at the site.

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. Specifically, the inspection identified many discrepancies between the subject source records (worksheets and radiology reports) and sponsor's data listings with respect to tumor measurements, tumor response assessments, and progression free survival assessment. Only a few representative examples are provided below.

A. Tumor Measurement Data had discrepancies for the following subjects and cycles:

1. Subject #1448: Cycle 3

The worksheet (source) documented Lesion #1 liver as 106 mm, the radiology scan documented a measurement of 10.6 cm (100.6mm), and the data listings had a measurement of 100.6 mm.

*In her response letter, Dr. Arce confirmed this measurement as 106 mm; there was a transcription error.*

2. Subject #1476: Baseline, Cycles 5, 7, 11. For example,

- a. For Cycle 5, the worksheet (source) documented Lesion #1 with a measurement of 17.1 mm, Lesion #2 with measurement of 15 mm, and Lesion #3 as 17.9 mm; the data listings documented values of 16.9 mm, 15.1 mm and 19.1 mm, respectively.

*In the response letter, Dr. Arce confirmed this as Lesion #1 17.1 mm; Lesion #2 15 mm; Lesion #3 17.9 mm as per review performed by the radiologist and PI. The cause of error is believed by Dr. Arce to be transcription.*

- b. For Cycle 7, the worksheet (source) documented Lesion #1 as 17.1 mm, the radiology report documented a value of 7.1 mm, and the data listing documented a value of 16.9 mm.

*In the response letter, Dr. Arce confirmed the measurement as 17.1 mm as per a review performed by the radiologist and PI. The cause of error is believed to be transcription.*

- c. For Cycle 11, the worksheet (source) and the radiology scan was missing for Lesion #1, #2, and #3. The data listings documented the following: Lesion #1: 15 mm; Lesion #2: 17 mm; Lesion #3: 18 mm.

*In the response letter, Dr. Arce stated that by mistake the subject had two CT scans during the same month, and a wrong date was provided so the source*

*data was not available during the inspection. The worksheet has now been corrected. No other information was provided.*

3. Subject #1539: Cycles 3, 5, 7, 9, and 11. For example:

- a. At Cycle 7, the worksheet (source) documented Lesion #1 and Lesion #2 as not measurable whereas the data listings documented a value of 4.9 mm for each lesion.

*In the response letter, Dr. Arce confirmed this as non-measurable. By query resolution, lesions that are too small to measure but are visible should be assigned a default of 5 mm.*

- b. At Cycle 9, the worksheet documented Lesion #1 and #2 as not visible, whereas the data listings had no data for Cycle 9.

*In the response letter, Dr. Arce confirmed this as absent according to the applicable RECIST category. According to the RECIST, measurement of non-target lesions should be followed as 'present' or 'absent' whereas target lesions should be recorded in the CRF in millimeters.*

4. Subject #1581: Cycles 3, 5, 7, 9, 11, 13, 16, and 19. For example,

- a. At Cycle 5, the worksheets (source) documented Lesion #1 (liver Seg 7) with a measurement of 22 mm, Lesion #2 (liver Seg 6) as 18 mm, and Lesion #3 (sternum) as 52 mm. The data listings documented Lesion #1 (sternum) 59 mm, Lesion #2 (liver) 24 mm, Lesion #3 (liver) 19.5 mm.

*In the response letter, Dr. Arce confirmed this as Lesion #1 (sternum) 52mm; Lesion #2 (liver) 22 mm; Lesion #3 (liver) 18mm. This was confirmed to be the correct measure after the review performed by the radiologist and the PI. The cause of error is believed to be transcription.*

- b. At Cycle 7, worksheets documented Lesion #1 (liver) as 17 mm, Lesion #2 (liver) as 13 mm and Lesion #3 (sternum) as 52.8 mm. The radiology report documented Liver seg 6 as 13 mm and Liver seg 7 as 17 mm. The data listings reported Lesion #1 (sternum) 59 mm, Lesion #2 (liver) 13 mm and Lesion #3 (liver) 17 mm.

*In the response letter, Dr. Arce confirmed this as Lesion #1 (sternum) 52.8 mm; Lesion #2 (liver) 17 mm; Lesion #3 (liver) 13 mm, after the review was confirmed by the radiologist and the PI. The cause of error is believed to be transcription. She stated the information would be updated in the medical notes and the CRF by October 15, 2017.*

B. Tumor Response Assessments had discrepancies for the following:

## 1. Subject #1448: Cycle 3

- a. The worksheet (source) reported response for Target Lesion as None, the radiology report documented response for Target Lesion as PD due to increase in size, and the data listings documented Target Lesion as SD.

*In the response letter Dr. Arce confirmed the correct response for the target lesion as PD, because the subject had new lesions. She stated the information would be updated in the medical notes and the CRF by October 15, 2017.*

## 2. Subject #1539: Cycles 5 and 7. For example:

At Cycle 5, the worksheet documented Overall Response as PR, and then changed to CR. The worksheet does not specify Target versus Non-Target Lesion response. The data listings reported Overall Response and Target Response as PR.

*In the response letter, Dr. Arce confirmed the correct response as CR. This was confirmed after the review performed by the radiologist and the PI. Data would be updated in the medical notes and the CRF by October 15, 2017.*

## 3. Subject #1581: Cycles 5, 7, 9, 11, 13, 16, and 19. For example:

- a. At Cycle 5 on 9/25/2015, on the worksheet (source) the documented Overall Response was SD, then changed to PR. The data listings documented Overall response as SD.

*In the response letter, Dr. Arce confirmed the disease progression as PR. This was confirmed after the review performed by the radiologist and the PI. Data would be updated in the medical notes and the CRF by October 15, 2017.*

- b. At Cycle 11 on 3/17/2016, the worksheet (source) documented Overall Response as SD, then was changed to PR. The data listings documented Overall Response as SD.

*In the response letter, Dr. Arce confirmed the correct response as PR. This was confirmed after the review performed by the radiologist and the PI. Data would be updated in the medical notes and the CRF by October 15, 2017.*

## 4. Subject 2066: Cycles 3, 5, 7, 9, 11, and 13 For example,

At Cycle 7 on 5/14/2016, the worksheet documented Overall Response as SD, whereas the data listings documented PR, and at Cycle 9 on 7/11/2016, the worksheet documented Overall Response as SD, whereas the data listings documented Overall Response as CR.

*In the response letter Dr. Arce confirmed the correct response as SD for Cycle 7 and SD for Cycle 9. This was confirmed after the review performed by the radiologist and the PI. Data would be updated in the medical notes and the CRF by October 15, 2017.*

*Reviewer Comments: Dr. Arce Salinas submitted a detailed response letter dated September 16, 2017 to the FDA 483, Inspectional Observations. The letter included the correct tumor measurements and disease progression assessments for the discrepancies that were listed in the FDA 483. According to Dr. Arce, the corrected measurements were confirmed after a review by the radiologist and the PI. Dr. Arce also stated that all corrections would be clarified in the e-CRF and medical notes by October 15, 2017.*

*Dr. Arce also outlined a comprehensive corrective action plan to prevent errors moving forward.*

*According to the primary reviewer in an email dated September 18, 2017, the database lock for primary efficacy analysis PFS occurred on March 14, 2017 and there should be no further changes to the trial database, unless the sponsor submits an updated PFS analysis. At Dr. Arce's site, the following three subjects appeared to have changes to their RECIST assessment:*

*Subject 1539 PR to CR*

*Subject 1581 SD to PR*

*Subject 2066 PR to SD, then CR to SD*

*It's unclear if these changes to the RECIST assessments will impact the primary efficacy analysis. Therefore, OSI recommends conducting a sensitivity analysis to determine its impact on the overall efficacy analysis.*

Note: The final EIR from the inspection of Dr. Arce was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

**3. Hiroji Iwata**  
**1-1 Kanokoden Chikusa-Ku**  
**Nagoya, Aichi 464-8681**

The inspection reviewed the conduct of clinical study 13Y-MC-JPBL (Monarch 2) at this site. Dr. Iwata was a moderate-range enroller, had high site efficacy results, a low number of serious adverse events (SAEs), low number of deaths, low number of protocol violations, and contributes to the low death rate in the Asia/Pacific compared to other regions. Dr. Iwata has ten IND studies in the COMIS database. No prior FDA

inspections were conducted at this site.

The site screened 13 subjects and enrolled 11 subjects. One subject completed the study, and the other subjects are currently being followed.

The inspection reported that the tumor assessments were performed by the clinical investigator, and a copy of the images was sent to a central laboratory, as per study requirements. However, the disease evaluation or progression assessment was based on the assessments made by the clinical investigator or sub-investigator.

The field investigator compared the data in the eCRF with the data listings for all subjects for: tumor measurement, disease progression response, adverse events, concomitant medications, randomization, progression-free survival time, and deviations. There were no discrepancies. The site initiation report and interim monitoring reports were reviewed and found to be adequate.

During the inspection, the field investigator compared the Listing of Tumor Measurements for Target Lesions with the image measurements in the subject's electronic medical records (EMR)/eCRF. The following inconsistencies were noted.

For Subject 1203, during Cycle 22, the pleura image of August 30, 2016 had tumor measurement of 7.16 mm, the data listings had measurement of 7.1 mm and the CRF had tumor measurement of 17.6 mm. For Subject 1614, during Cycle 5, the CT scan liver image of October 8, 2015 had tumor measurement of 8.68 mm, the data listings had a measurement of 8.6 mm, and the CRF documented a measurement of 10.3 mm; and for Subject 1614, at Cycle 13, the the CT scan image of the thoracic lymph node had a measurement of 6.14 mm, whereas the data listings and the eCRF had a measurement of 7.8.

*Reviewer Comments: Subject 1203 had tumor measurements for 2 lesions at screening, and Cycles, 3, 5, 7, 9, 11, 13, 16, 19, 22, 25 and 28. Subject 1614 had tumor measurements for 3 lesions at screening and Cycles 3, 5, 7, 9, 11, 13 16 and 19.*

*The inconsistencies are only a few, and unlikely to have a significant impact on the reliability of the data.*

*Reviewer Comments: The above discrepancies are unlikely to impact the efficacy analysis for the study. : It is recommended the review division evaluates the significance of the inconsistencies described above on efficacy analysis.*

#### **4. Sung-Bae Kim**

88, Olympic-ro 43-Gil, Songpa-gu  
**Seoul, Korea 5505**

The inspection reviewed the conduct of Protocol 13Y-MC-JPBL (Monarch 2) at this site. Dr. Sung-Bae Kim has ten IND studies in the COMIS database. She had a

previous inspection in April 2012 that was classified as NAI.

This site screened 13 subjects and enrolled 11 subjects. The field investigator compared source documents and data in the electronic case report forms (eCRF), with the data listings provided with the assignment for all subjects with respect to: tumor sizes, disease progression response, primary efficacy, adverse events, concomitant medications, randomization, progression-free survival time, and protocol deviations.

Source data consisted of electronic medical records, paper records such as subject diary, image worksheets, and test article records. The majority of the study data were collected in electronic medical records.

Other areas covered during the inspection included: monitoring, financial disclosure forms, Institutional Review Board (IRB) communication, informed consent documents (ICD), test article records (accountability, storage, and dispensation), delegation log, and general protocol adherence.

No significant observations were noted, and no Form FDA 483, Inspectional Observations was issued. The study was conducted adequately. The data from Dr. Kim's associated with Study 13Y-MC-JPBL (Monarch 2) site appear reliable based on available data.

**5. Sara Tolaney**  
**450 Brookline Ave**  
**Harvard Med School**  
**Boston, MA 02215**

The inspection reviewed the conduct of clinical studies 13Y-MC-JPBL (Monarch 2) and 13Y-MC-JPBN (Monarch 1). Dr. Tolaney had high enrollment in the JPBN study, and conducted both pivotal studies. Dr. Sara Tolaney has ten IND studies in the COMIS database, and no prior inspections.

For 13Y-MC-JPBN (Monarch 1) the site screened 21 subjects and enrolled 17 subjects. (15 at Dana Farber Cancer Institute and 2 at Beth Israel Deaconess Medical Center). The first subject was screened on October 1, 2014, signed the informed consent document (ICD) on October 3, 2014, and was administered test article on October 17, 2014. Sixteen subjects had progression of disease, seven of which were deaths; one subject withdrew consent after a Serious Adverse Event (SAE). At the time of the inspection, no subjects were actively enrolled.

The inspection reviewed all adverse events (AEs) and there did not appear to be under-reporting of Serious Adverse Events (SAEs). The inspection spot-checked laboratory data, concomitant medications, diagnostic testing results, and study visit dates and found no discrepancies.

Source documentation was compared with the data listings, to verify: 1) protocol adherence; 2) subject eligibility; 3) administration of the investigational product or placebo;

4) concomitant medications; 5) key personnel involved in collecting and analyzing data; and 6) adverse event reporting.

All subjects met the inclusion and exclusion criteria, and the primary efficacy data was verifiable. Adverse events did not appear to be under-reported.

The inclusion and exclusion criteria were met for all of subjects and protocol deviations were properly documented and reported.

The subject binders were in good condition. The Informed Consent Documents (ICD), central and local laboratory reports, demographic information, subject test article diaries, and hand-written study questionnaires were available for review. No issues were found.

For Study 13Y-MC-JPBL (Monarch 2), six subjects were enrolled; there were no screen failures. The first subject signed the ICD on April 16, 2015, and began test article on April 23, 2015. One subject died, and four subjects were taken off the active study due to disease progression. At the time of the inspection, one subject was still actively enrolled and receiving study drug.

All subjects met the inclusion and exclusion criteria, all AEs and SAEs appeared to be appropriately reported. Other data including laboratory reports, concomitant medications, diagnostic testing results, and study visit dates were spot checked and no discrepancies were found. There was adequate documentation that all subjects were alive and available during their stated participation in the study.

The data from Dr. Tolaney's site associated with Study 13Y-MC-JPBL (Monarch 2) and Study 13Y-MC-JPBN (Monarch 1) appear reliable based on available data.

**6. Maura Dickler**  
**1275 York Ave**  
**New York, NY 10065**

The inspection audited Protocol 13Y-MC-JPBL (Monarch 2) and Protocol 13Y-MC-JPBN (Monarch 1). Dr. Dickler has ten IND studies in the COMIS database, and no prior inspections. The reason for inspecting Dr. Dickler was that she had high enrollment in the JPBN study, the results drove efficacy for that study, and a sponsor audit was conducted at her site. She also conducted both studies.

Protocol JPBL:

Eight subjects were screened and six subjects were enrolled. The first subject signed the informed consent document (ICD) on 07/28/15 and the last subject signed the ICD on 10/09/15. Two subjects remained on study treatment at the time of the inspection.

The field investigator conducted a comprehensive review for all six subjects to confirm compliance with the protocol. The source documents were compared against the sponsor data listings provided in the assignment, for treatment assignment,

discontinuations, adverse events (AEs), serious adverse events (SAEs), tumor measurements, overall tumor response, protocol violations, and concomitant medications. The field investigator also reviewed the following items: monitor site visit logs, informed consent documents, FDA Forms 1572s, financial disclosure forms, IRB approval forms, SAEs and AEs for completeness and timely reporting, visit dates, and RECIST response assessment forms.

The field investigator identified two subjects who did not meet enrollment criteria in that they did not have progression of disease more than one year from completion of adjuvant endocrine therapy. Several minor discrepancies were noted between subjects' source records and electronic-Case Report Forms (e-CRFs). For one subject, an AE was not reported in the e-CRF.

The Tumor Measurements and Overall Tumor Response line listings were compared against the six enrolled subjects' source records, specifically their RECIST response assessment forms. Tumor measurements, visit dates and overall response were verified at the site.

Protocol JPBN:

For this study, 19 subjects were screened and 17 subjects were enrolled. All subjects completed the study. The first subject signed the ICD on 10/20/2014 and the last subject signed the ICD on 3/30/2015.

The field investigator completed a comprehensive review for all 17 subjects. The source documents were corroborated with the sponsor's data listings provided in the assignment. Tumor measurements, visit dates, and overall response as defined by RECIST 1.1 were verified at the site. Raw data for the study was contained in electronic medical records (EMR) and included laboratory results, RECIST response assessment forms, toxicity grading sheets, eligibility checklists, electrocardiograms (ECGs), CT scans, MRI's, physician and nurse notes, progress notes, pathology reports, and questionnaires. All subjects met the inclusion and exclusion criteria. Several discrepancies were observed between source records, electronic data capture (EDC)/e-CRFs, and the sponsor's data listings. For six subjects, all AEs were not reported in the EDC/eCRFs and did not appear in the data listings.

A FDA Form 483 was issued at this site:

Failure to report promptly to the sponsor adverse effects that may be regarded as caused by an investigational drug. For example,

- a) For Protocol 13Y-MC-JPBL, Subject 1852 had headache dated 7/30/2016 documented in source records.
- b) For Protocol 13Y-MC-JPBN, Subject 1220 had dysgeusia dated 5/26/2015 and skin pigmentation on hands dated 6/1/2015 documented in source records.

- c) For Protocol 13Y-MC-JPBN, Subject 1160 had fatigue dated 6/3/2015, and hair thinning dated 5/6/2015 documented in source records.

These AEs were not reported in the EDC/e-CRF and were not documented in the sponsor's data listings.

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. For example,

- a) For protocol 13Y-MC-JPBL, for Subject #1852, Nexium was documented in the source records, but not documented in the EDC/e-CRF. The medication was added on 7/20/2017.
- b) For protocol 13Y-MC-JPBN, concomitant medications were documented in source records, but not recorded in the EDC/e-CRF. For example,
- c) For Subject #1147, source documents documented Halog topical cream for skin rash on 10/8/2015 and rivaroxaban 20 mg for prevention of blood clots on 10/8/2015.
- d) For Subject #1202, source records documented Benicar HCT for blood pressure on 4/1/2015, Vitamin D3 supplement on 4/1/2015, oxycodone 5 mg for pain on 4/1/2015, and Senokot S for constipation on 4/1/2015.

These concomitant medications were not documented in the EDC/e-CRF. The Clinical Research Coordinator stated that at the beginning of the study the monitor told the site that concomitant medication review was not a requirement.

- e) For Protocol 13Y-MC-JPBL, for Subject #1852, the toxicity grading record showing headache from 7/30/2016 was requested, and not provided.
- e) For Protocol 13Y-MC-JPBN, for Subject #1131, the medication list source record showing Protonix and Imodium was requested and not provided.

*Dr. Dickler provided a written response to the Form FDA 483 inspectional observations dated August 16, 2017. In her letter, she provided a comprehensive correction action plan to ensure that the above findings would not occur going forward. She also provided copies of the requested documents listed in Observation 3 for Subject #1852 and Subject @1131. She stated that there was a verbal miscommunication pertaining to these documents during the inspection. In general, the protocol violations found at this site should not importantly impact overall study outcomes. Neither the adverse events that were not reported nor the unreported concomitant medications placed the subjects at important risk.*

Although violations were noted that included under-reporting of adverse events (AEs), the nature of the AEs do not appear significant, and are unlikely to have a significant impact on subject safety. Likewise, for the unreported concomitant medications, OSI

does not consider this finding significant, and considers their omission as unlikely to have an impact on subject safety.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H., Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA #208716  
OHOP/DOP1 Division Director (Acting)/Julia Beaver  
OHOP/Team Leader/ Laleh Amiri-Kordestani  
OHOP/Clinical Reviewer/Lynn Howie  
OHOP/Regulatory Project Manager/Janice Kim  
OSI/Office Director /David Burrow  
OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCPAB/Team Leader/Susan Thompson  
OSI/DCCE/GCP Reviewer/Sharon Gershon  
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague  
OSI/Database PM/Dana Walters

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/s/  
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SHARON K GERSHON  
09/26/2017

SUSAN D THOMPSON  
09/26/2017

KASSA AYALEW  
09/26/2017

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

---

**Date of This Memorandum:** September 21, 2017  
**Requesting Office or Division:** Division of Oncology Products 1 (DOP1)  
**Application Type and Number:** NDA 208716  
**Product Name and Strength:** Verzenio (Abemaciclib) Tablets  
50 mg, 100 mg, 150 mg, 200 mg  
**Applicant/Sponsor Name:** Eli Lilly and Company (Eli Lilly)  
**Submission Date:** September 1, 2017 and September 20, 2017  
**OSE RCM #:** 2017-947-1  
**DMEPA Safety Evaluator:** Grace P. Jones, PharmD, BCPS  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD, BCPS

---

## 1 PURPOSE OF MEMO

The Division of Oncology Products 1 (DOP1) requested that we review the revised container labels and carton labeling submitted September 1, 2017, and prescribing information (PI) submitted September 20, 2017 for Verzenio (abemaciclib) tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

(b) (4)

## 2 CONCLUSION

The revised container labels, carton labeling, and prescribing information (PI) for Verzenio are acceptable from a medication error perspective. We have no further recommendations at this time.

---

<sup>a</sup> Jones GP. Label and Labeling Review for Verzenio (NDA 208716). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 25. RCM No.: 2017-947.

<sup>b</sup> Eli Lilly and Company. Information Request. Abemaciclib tablets, NDA 208716. Indianapolis (IN): Eli Lilly and Company; 2017 SEP 20

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/s/  
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GRACE JONES

09/21/2017

CHI-MING TU

09/21/2017

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

---

NDA# 208716  
Product Name: Abemaciclib

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PMR Description: 3254-1 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 abemaciclib 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.

---

|                              |                            |                   |
|------------------------------|----------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>06/30/2018</u> |
|                              | Trial Completion:          | <u>06/30/2021</u> |
|                              | Final Report Submission:   | <u>12/31/2021</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Diarrhea occurred in 86 to 90% of patients enrolled in the registration trials, including severe cases in 13 to 20% of patients when the recommended dose of abemaciclib (150 mg BID or 200 mg BID) was administered orally with or without food, and resulted in dose modifications and dose interruptions in 25% of patients. The food effect trial showed no effect of food on the pharmacokinetics of abemaciclib. There was a dose-response relationship for diarrhea, suggesting that diarrhea may be due to local effects in the gastrointestinal tract prior to drug absorption. Administration of abemaciclib at the recommended dose (150 mg BID or 200 mg BID) with meals may decrease GI toxicity and diarrhea compared to administration of abemaciclib in a modified fasted condition or as recommended, without regard to food.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is determine whether administration of abemaciclib with meals can improve the tolerability of abemaciclib by decreasing the incidence of serious diarrhea related dose reductions and dose interruptions, compared to administration of abemaciclib in a modified fasted condition or, as recommended, without regard to food.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Evaluate the incidence of dose reductions and dose interruptions due to diarrhea when abemacicib is administered at the recommended dosage (150 mg BID and 200 mg BID) with meals, compared to abemaciclib taken in the modified fasted condition, and when it is administered without regard to food in patients. This evaluation may be done in an ongoing or new clinical trial.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☒ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?

Submit a final report and datasets from an ongoing or new clinical trial to evaluate the incidence

of dose reductions and dose interruptions due to severe diarrhea when abemaciclib 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.

PMR Schedule Milestones:

Final Protocol Submission: 06/30/2018

Trial Completion: 06/30/2021

Final Report Submission: 12/31/2021

☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208716  
Product Name: Abemaciclib

PMC Description: 3254-2 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”

|                              |                           |            |
|------------------------------|---------------------------|------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission | 04/01/2014 |
|                              | Trial Completion:         | 12/31/2021 |
|                              | Final Report Submission:  | 06/30/2022 |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

At the time of approval the final OS analysis will not have been reached

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Not a PMR

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

These data are being collected as part of the ongoing study that is being used for registration.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  
Follow up survival data for safety and efficacy assessment
  - ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
  - ☐ Immunogenicity as a marker of safety
  - ☐ Other (provide explanation)
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
  - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - ☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - ☐ Dose-response study or clinical trial performed for effectiveness
  - ☐ Nonclinical study, not safety-related (specify)
- 

- ☐ Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

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|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA#                       | 208716                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Product Name:              | Abemaciclib                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| PMC Description:<br>3254-3 | Conduct <b>Physiologically based Pharmacokinetic modeling (PBPK)</b> 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 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. |

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PMR/PMC Schedule Milestones:

Final Report Submission:

02/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Coadministration of a strong CYP3A4 inducer decreased total free drug exposure of abemaciclib plus its active metabolites by 60%. The effect of moderate CYP3A4 inducers is unknown, and dose adjustment may be needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the drug-drug interaction assessment is to determine how to dose of abemaciclib in patients requiring concomitant use of a moderate CYP3A4 inducer.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a clinical 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.

Required

- ☐ Observational pharmacoepidemiologic study  
☐ Registry studies  
☐ Primary safety study or clinical trial  
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
☐ Thorough Q-T clinical trial  
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
☐ Pharmacokinetic studies or clinical trials  
☐ Drug interaction or bioavailability studies or clinical trials  
☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials  
☐ Immunogenicity as a marker of safety  
☐ Other (provide explanation)
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)  
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
☐ Dose-response study or clinical trial performed for effectiveness  
☐ Nonclinical study, not safety-related (specify)

- 
- ☒ Other  
Drug interaction trial
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?  
☒ Are the objectives clear from the description of the PMR/PMC?  
☒ Has the applicant adequately justified the choice of schedule milestone dates?  
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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CHRISTINA D MARSHALL  
09/19/2017

KATHERINE M FEDENKO  
09/19/2017

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

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

**Memorandum**

**Date:** September 1, 2017

**To:** Julia Beaver, M.D., Acting Director  
Division of Oncology Products 1 (DOP1)

Janice Kim, PharmD, Regulatory Project Manager, (DOP1)

William Pierce, PharmD, Associate Director for Labeling, (DOP1)

**From:** Kevin Wright, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Brian Tran, PharmD, MBA, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Verzenio<sup>™</sup> (abemaciclib) tablets, for oral use

**NDA:** 208716

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In response to DOP1's consult request dated May 17, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton labeling for the original NDA submission for Verzenio<sup>™</sup> (abemaciclib) tablets, for oral use.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Janice Kim) on August 17, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover.

OPDP has reviewed the attached proposed carton labeling submitted by the Sponsor to the electronic document room on September 1, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright of OPDP reviewer at (301) 796-3621 or [kevin.wright@fda.hhs.gov](mailto:kevin.wright@fda.hhs.gov).

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

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/s/  
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KEVIN WRIGHT  
09/01/2017

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 28, 2017

To: Julia Beaver, MD  
Acting Director  
**Division of Oncology Products 1 (DOP1)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Kevin Wright, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): VERZENIO (abemaciclib)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 208716

Applicant: Eli Lilly and Company

## 1 INTRODUCTION

On May 5, 2017, Eli Lilly and Company, submitted for the Agency's review an original New Drug Application (NDA 208716) seeking approval for the use of abemaciclib, tablets, for oral use, in combination with fulvestrant for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer in women whose disease has progressed following endocrine therapy, and for use as monotherapy in the treatment of HR+, HER2- metastatic breast cancer in (b) (4) whose disease has progressed following endocrine therapy and (b) (4) prior chemotherapy (b) (4) in the metastatic setting. On June 8, 2017, the Agency granted the Applicant the proprietary tradename of VERZENIO.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP 1) on May 31, 2017, and May 17, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for abemaciclib, tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft VERZENIO (abemaciclib) PPI received on May 5, 2017, and received by DMPP and OPDP on August 17, 2017.
- Draft VERZENIO (abemaciclib) Prescribing Information (PI) received on July 31, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 17, 2017.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/  
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SHAWNA L HUTCHINS  
08/28/2017

KEVIN WRIGHT  
08/28/2017

BARBARA A FULLER  
08/28/2017

LASHAWN M GRIFFITHS  
08/28/2017

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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

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|                                       |                                                                 |
|---------------------------------------|-----------------------------------------------------------------|
| <b>Date of This Review:</b>           | July 25, 2017                                                   |
| <b>Requesting Office or Division:</b> | Division of Oncology Products 1 (DOP1)                          |
| <b>Application Type and Number:</b>   | NDA 208716                                                      |
| <b>Product Name and Strength:</b>     | Verzenio (Abemaciclib) Tablets<br>50 mg, 100 mg, 150 mg, 200 mg |
| <b>Product Type:</b>                  | Single-ingredient Product                                       |
| <b>Rx or OTC:</b>                     | Rx                                                              |
| <b>Applicant/Sponsor Name:</b>        | Eli Lilly and Company (Eli Lilly)                               |
| <b>Submission Date:</b>               | May 5, 2017 and June 30, 2017                                   |
| <b>OSE RCM #:</b>                     | 2017-947                                                        |
| <b>DMEPA Primary Reviewer:</b>        | Grace P. Jones, PharmD, BCPS                                    |
| <b>DMEPA Team Leader:</b>             | Chi-Ming (Alice) Tu, PharmD, BCPS                               |

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## 1 REASON FOR REVIEW

As part of the review of the submission under NDA 208716, Verzenio (abemaciclib) tablets, the Division of Oncology Products 1 (DOP1) requested that we review the submitted container labels, carton labeling, and prescribing information (PI) for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review |                                               |
|------------------------------------------------------------------|-----------------------------------------------|
| Material Reviewed                                                | Appendix Section<br>(for Methods and Results) |
| Product Information/Prescribing Information                      | A                                             |
| Previous DMEPA Reviews                                           | B – N/A                                       |
| Human Factors Study                                              | C – N/A                                       |
| ISMP Newsletters                                                 | D – N/A                                       |
| FDA Adverse Event Reporting System (FAERS)*                      | E – N/A                                       |
| Other                                                            | F – N/A                                       |
| Labels and Labeling                                              | G                                             |

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed Verzenio container labels (pull out blister cards) and carton labeling (blister card sleeves) forms the proposed blister packaging configuration. We received physical representative samples of the blisters based on our June 21, 2017 information request.<sup>a,b</sup>

Our review of the proposed container labels and carton labeling identified that information located on the left most side of the pull out blister card is obstructed by the blister card sleeve. Thus, the text, “PUSH tablet through the card to the other side of the package” located on the front left side of the pull out blister card and the proposed product’s proprietary name, strength, and dose on the back left side are not readily visible when the pull out blister card is pulled out. (b) (4)

<sup>a</sup> See DARRTS Information Request, dated 6/22/2017.

<sup>b</sup> The response to the Information Request is available from:  
<\\cdsesub1\evsprod\nda208716\0022\m1\us\cover.pdf>

(b) (4)

Our review of the proposed PI identified that the table provided in the How Supplied/Storage and Handling Section can be revised to improve clarity and to prevent misinterpretation and confusion. In addition, we provide a minor edit to (b) (4)

## 4 CONCLUSION & RECOMMENDATIONS

The proposed Verzenio container labels (pull out blister cards) and the prescribing information may be improved to ensure safe use of the proposed product. We provide specific recommendations in Section 4.1 and 4.2 below.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Prescribing Information (PI)

##### a. How Supplied/Storage and Handling

- i. The table format as currently presented may cause confusion. Consider revising Section 16.1 How Supplied Section to a text format that separates out tablet description from information that prescribers need to order a specific blister dose pack when prescribing Verzenio. For example, revise Section 16.1 to read:

VERZENIO 50 mg tablets are (b) (4) oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

VERZENIO 100 mg tablet are (b) (4) oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

VERZENIO 150 mg tablets are (b) (4) oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

VERZENIO 200 mg tablets are (b) (4) oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

VERZENIO tablets are supplied in 7-day dose pack configurations as follows:

(b) (4)

- 200 mg dose pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (200 mg twice daily)  
NDC 0002-6216-54
- 150 mg dose pack (14 tablets) – each blister pack contains 14 tablets (150 mg per tablet) (150 mg twice daily)  
NDC 0002-5337-54
- 100 mg dose pack (14 tablets) – each blister pack contains 14 tablets (100 mg per tablet) (100 mg twice daily)  
NDC 0002-4815-54
- 50 mg dose pack (14 tablets) – each blister pack contains 14 tablets (50 mg per tablet) (50 mg twice daily)  
NDC 0002-4483-54

## 4.2 RECOMMENDATIONS FOR ELI LILLY

We recommend the following be implemented prior to approval of this NDA:

### A. Container Labels – Pull Out Blister Cards

1. Revise the pull out blister cards so that the information, “PUSH tablet through the card to the other side of the package” and the product name, strength, and dose information on the backside are readily visible. As currently proposed and based on the physical sample blister pack submitted to the Agency, when the pull out blister card is fully pulled out, the text that is located on the leftmost side is not readily visible.

### B. Carton Labeling – Blister Card Sleeves

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Verzenio that Eli Lilly submitted on June 30, 2017.

| Table 2. Relevant Product Information for Verzenio |                                                                                                                                                                                                                                                                          |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial Approval Date                              | N/A                                                                                                                                                                                                                                                                      |
| Active Ingredient                                  | Abemaciclib                                                                                                                                                                                                                                                              |
| Indication                                         | (b) (4)                                                                                                                                                                                                                                                                  |
| Route of Administration                            | Oral                                                                                                                                                                                                                                                                     |
| Dosage Form                                        | Tablets                                                                                                                                                                                                                                                                  |
| Strength                                           | 50 mg, 100 mg, 150 mg, 200 mg                                                                                                                                                                                                                                            |
| Dose and Frequency                                 | Recommended dose in combination with fulvestrant is 150 mg orally, twice daily.<br>Recommended dose as a single agent is 200 mg orally, twice daily.<br>If dose reduction is necessary, reduce dose by 50 mg at a time                                                   |
| How Supplied                                       | (b) (4)<br><ul style="list-style-type: none"><li>• 200 mg dose (one 200 mg tablet), 14 tablets</li><li>• 150 mg dose (one 150 mg tablet), 14 tablets</li><li>• 100 mg dose (one 100 mg tablet), 14 tablets</li><li>• 50 mg dose (one 50 mg tablet), 14 tablets</li></ul> |
| Storage                                            | Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).                                                                                                                                                                                   |

|                          |                                                              |
|--------------------------|--------------------------------------------------------------|
| <b>Container Closure</b> | <b>Packaged in a blister presentation</b> (b) (4)<br>(b) (4) |
|--------------------------|--------------------------------------------------------------|

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>c</sup> along with postmarket medication error data, we reviewed the following Verzenio labels and labeling submitted by Eli Lilly on May 5, 2017 and June 30, 2017.

- Container labels
- Carton labeling
- Prescribing Information (Image not shown) – submitted on June 30, 2017

### **G.2 Label and Labeling Images**

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<sup>c</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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GRACE JONES  
07/25/2017

CHI-MING TU  
07/25/2017

# REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208716

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** Verzenio (abemaciclib) tablets

**Applicant:** Eli Lilly

**Receipt Date:** May 5, 2017

**Goal Date:** January 5, 2018

## 1. Regulatory History and Applicant's Main Proposals

Eli Lilly has submitted a new NDA 208716 for abemaciclib

(b) (4)

the Applicant is requesting priority review. The associated IND 106100 received breakthrough therapy designation. This application was submitted on May 5, 2017, and final proposed labeling will be provided on or before July 5, 2017, and will include complete MONARCH 2 study data as well as data from the newly completed clinical pharmacology study, JPCK. Eli Lilly will also submit updated Module 2 summary document that include MONARCH 2 study and related information no later than July 5, 2017.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

## 3. Conclusions/Recommendations

The following deficiency will be conveyed to the Applicant:

1. In Section 17, the introductory statement currently reads: "Advise patients to read the FDA-approved Patient Information. (b) (4) The term "patients" should be singular, not plural (b) (4)

## Selected Requirements of Prescribing Information

### 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix for a sample tool illustrating Highlights format.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.  
**Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Headings in HL must be presented in the following order:

| Heading              | Required/Optional |
|----------------------|-------------------|
| • Highlights Heading | Required          |

## Selected Requirements of Prescribing Information

|                                                   |                                                       |
|---------------------------------------------------|-------------------------------------------------------|
| • <b>Highlights Limitation Statement</b>          | Required                                              |
| • <b>Product Title</b>                            | Required                                              |
| • <b>Initial U.S. Approval</b>                    | Required                                              |
| • <b>Boxed Warning</b>                            | Required if a BOXED WARNING is in the FPI             |
| • <b>Recent Major Changes</b>                     | Required for only certain changes to PI*              |
| • <b>Indications and Usage</b>                    | Required                                              |
| • <b>Dosage and Administration</b>                | Required                                              |
| • <b>Dosage Forms and Strengths</b>               | Required                                              |
| • <b>Contraindications</b>                        | Required (if no contraindications must state “None.”) |
| • <b>Warnings and Precautions</b>                 | Not required by regulation, but should be present     |
| • <b>Adverse Reactions</b>                        | Required                                              |
| • <b>Drug Interactions</b>                        | Optional                                              |
| • <b>Use in Specific Populations</b>              | Optional                                              |
| • <b>Patient Counseling Information Statement</b> | Required                                              |
| • <b>Revision Date</b>                            | Required                                              |

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

## Selected Requirements of Prescribing Information

“**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:**

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

**Comment:**

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

### Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:**

### Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

**Comment:**

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

*Comment:*

### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

*Comment:*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:*
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

|                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------|
| <b>BOXED WARNING</b>                                                                                                   |
| <b>1 INDICATIONS AND USAGE</b>                                                                                         |
| <b>2 DOSAGE AND ADMINISTRATION</b>                                                                                     |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                                                                                    |
| <b>4 CONTRAINDICATIONS</b>                                                                                             |
| <b>5 WARNINGS AND PRECAUTIONS</b>                                                                                      |
| <b>6 ADVERSE REACTIONS</b>                                                                                             |
| <b>7 DRUG INTERACTIONS</b>                                                                                             |
| <b>8 USE IN SPECIFIC POPULATIONS</b>                                                                                   |
| 8.1 Pregnancy                                                                                                          |
| 8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery") |
| 8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")          |
| 8.4 Pediatric Use                                                                                                      |
| 8.5 Geriatric Use                                                                                                      |
| <b>9 DRUG ABUSE AND DEPENDENCE</b>                                                                                     |
| 9.1 Controlled Substance                                                                                               |
| 9.2 Abuse                                                                                                              |
| 9.3 Dependence                                                                                                         |
| <b>10 OVERDOSAGE</b>                                                                                                   |
| <b>11 DESCRIPTION</b>                                                                                                  |
| <b>12 CLINICAL PHARMACOLOGY</b>                                                                                        |
| 12.1 Mechanism of Action                                                                                               |
| 12.2 Pharmacodynamics                                                                                                  |
| 12.3 Pharmacokinetics                                                                                                  |
| 12.4 Microbiology (by guidance)                                                                                        |
| 12.5 Pharmacogenomics (by guidance)                                                                                    |
| <b>13 NONCLINICAL TOXICOLOGY</b>                                                                                       |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility                                                              |
| 13.2 Animal Toxicology and/or Pharmacology                                                                             |
| <b>14 CLINICAL STUDIES</b>                                                                                             |
| <b>15 REFERENCES</b>                                                                                                   |
| <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>                                                                            |
| <b>17 PATIENT COUNSELING INFORMATION</b>                                                                               |

**Comment:**

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

**Comment:**

#### BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

**Comment:**

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

**Comment:**

#### ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:**

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

**NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:** The current statement says: "Advise patients to read the FDA-approved Patient Information." (b) (4) The term "patients" should be singular, not plural (b) (4)

**YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE H KIM  
07/21/2017

CHRISTY L COTTRELL  
07/21/2017

## Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

|                                    |                                                              |
|------------------------------------|--------------------------------------------------------------|
| <b>NDA</b>                         | 208716                                                       |
| <b>Brand Name</b>                  | VERZENIO                                                     |
| <b>Generic Name</b>                | Abemaciclib                                                  |
| <b>Sponsor</b>                     | Eli Lilly and Company                                        |
| <b>Indication</b>                  | Treatment of Cancer                                          |
| <b>Dosage Form</b>                 | (b) (4)                                                      |
| <b>Drug Class</b>                  | small molecule CDK4/6 inhibitor                              |
| <b>Therapeutic Dosing Regimen</b>  | 200 mg Q12H                                                  |
| <b>Duration of Therapeutic Use</b> | Chronic                                                      |
| <b>Maximum Tolerated Dose</b>      | 200 mg Q12H or a single dose of 400 mg in healthy volunteers |
| <b>Submission Number and Date</b>  | 5/11/2017                                                    |
| <b>Review Division</b>             | DOP1                                                         |

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

The results from the healthy volunteer study reviewed and preclinical and clinical studies included in the development program supports concluding that abemaciclib does not cause large mean increases in the QTc interval (i.e. 20 ms).

The relationship between QTc prolongation and abemaciclib exposure was assessed in a single ascending dose study in healthy volunteers (I3Y-MC-JPCA). The study was planned to include doses up to 900 mg, but due to observed adverse events at dose level below 900 mg (i.e. 600 mg) the 900 mg dose level was not studied. In addition, the study did not include a positive control or sufficiently high exposures to waive the requirement for assay sensitivity per ICH E14 Q&A (R3), and can therefore not support excluding small mean increases in the QTc interval (i.e. 10 ms). Analysis of the ECG/PK data collected in the study did not reveal a relationship between the QTc interval and abemaciclib or metabolite (M2 and M20) concentrations with an upper bound at the  $C_{max}$  of the highest dose below 10 ms. The observed upper bound less than 10 ms, can support excluding large mean increases (i.e. 20 ms) in the QTc interval, if the clinically relevant exposures are covered for all moieties (ICH E14 Q&A 6.1). Exclusion of large mean increases is appropriate for abemaciclib based on the indication sought. While the  $C_{max}$  for the 600 mg dose in this study covers the  $C_{max,ss}$  in patients for the parent drug, this is

not the case for the two metabolites: M2 and M20 as the  $C_{\max,ss}$  in patients is 1.3-fold (M2) and 1.5-fold (M20) higher compared to the observed  $C_{\max}$  for the 600 mg dose in the healthy volunteer study. Of note, the worst case exposure scenario for abemaciclib is concomitant use with a CYP3A4 inhibitor based on a dedicated DDI study with clarithromycin, which showed a ~3.4-fold increase in abemaciclib exposure. Lastly, no QTc values greater than 480 ms or change from baseline greater than 60 ms ( $1 \Delta QTc > 30$  ms) was observed in this study.

In addition to the healthy volunteer study, the impact on the QTc interval was also assessed in patient studies at the MTD dose, which showed few QTc outliers (no  $\Delta QTc > 60$  and 2 QTc values  $> 500$  ms across all three studies) consistent with the healthy volunteer study.

The ability of abemaciclib and the M2 and M20 metabolites to block the hERG potassium channel was evaluated in a preclinical study and the results of this study did not suggest a potential to inhibit the hERG potassium channel for abemaciclib, M2 or M20.

Taken all altogether, it does not appear that abemaciclib causes large mean increases in the QTc interval.

## 2 PROPOSED LABEL

### Cardiac Electrophysiology

(b) (4)

*Reviewer's comments: The QT-IRT is providing proposed labeling language below, which is a suggestion only. We defer final labeling decisions to the Division.*

### Cardiac Electrophysiology

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib is not expected to cause large mean increases (i.e. 20 ms) in the QTc interval.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

VERZENIO™ (abemaciclib) is proposed for the following indication:

(b) (4)

(b) (4)

### 3.2 MARKET APPROVAL STATUS

Abemaciclib is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

In in vitro studies, abemaciclib and its major active metabolites M2 and M20 did not demonstrate blockade of the current produced by the human ether-a-go-go-related gene (hERG) potassium channel expressed in mammalian cells.

In the cardiovascular safety pharmacology study, Ventricular premature complexes (VPCs) and paroxysmal ventricular tachycardia (VT) occurred in 1 of 8 dogs given 10mg/kg, a dose that exceeded the maximum tolerated dose (MTD) in the 28-day repeat dose toxicity study. These arrhythmias were observed at several time points between 22 and 48 hours postdose. Although parent drug is detectable during this period, the occurrence of VT did not correlate with maximum plasma level of LY2835219. No waveform abnormalities or blood pressure changes were associated with this arrhythmia. Based upon the incidence in a single animal and the delayed onset, the VT was likely due to ventricular irritation originating from the insertion site of the left ventricular pressure transducer and/or positive electrocardiogram electrode. However, because the arrhythmia occurred only at the highest dose of LY2835219, it cannot be ruled out as a potential compound-related effect. No corrected QT interval (QTc) prolongation was observed in dogs following single dose administration up to 10 mg/kg. Exposure (C<sub>max</sub>) in dogs after a single 10 mg/kg dose is very similar to the human C<sub>max</sub> after a single 200 mg dose.

### 3.4 PREVIOUS CLINICAL EXPERIENCE

*Summary included below is an excerpt of the summary of clinical safety in patient studies.*

#### **JPBA**

Study JPBA evaluated changes in QTc from predose to steady-state abemaciclib exposure in patients. ECGs were performed at baseline and during Cycle 1 at the following times: predose, 2 and 4 hours postdose on Day -3; on Day -2 and Day -1; and predose and 2 and 4 hours postdose on Day 15. Increases in QTcF were observed from predose on Day -3 to predose on Day 15. The majority of these patients (n=72) experienced an increase in QTcF from 0 to 30 msec. Four patients experienced an increase in QTcF  $\geq 30$  msec, and no patients experienced an increase  $\geq 60$  msec (Table APP.2.7.4.52). Twenty-five patients had ECGs with treatment emergent QTcF interval abnormalities (including increases in QTcF  $>30$  msec and  $\leq 60$  msec). Ten of these patients had treatment-emergent QTcF interval abnormalities defined as a postdose QTcF  $>450$  msec for males and  $>470$  msec for females (Table APP.2.7.4.53).

Although increases were noted, the results of the ECG and safety data assessments did not provide clear evidence of a clinically significant change in QT/QTcF following the administration of abemaciclib in patients with advanced cancer. Due to limitations in data collection for baseline adjustments, no definitive conclusions can be made about the

relationship between change in QTcF interval and drug concentration based on Study JPBA data.

There were no deaths due to cardiac disorders or selected non-cardiac disorders (syncope, seizure, or hypokalemia) during the study. Across 33 patients who participated in the dose escalation phase (Part A), no patient experienced an SAE due to cardiac disorders or selected non-cardiac episodes (syncope, seizure, or hypokalemia). Across 173 patients who participated in Parts B through F, 8 patients experienced cardiac-related disorders and non-cardiac episodes. These events were not considered related to abemaciclib treatment.

### **JPBC**

In Study JPBC, an open-label, dose-escalation study in 12 patients, 12-lead ECGs were collected at baseline and during Cycle 1 at the following times: predose and 2, 4, 6, and 8 hours postdose on Day -3; on Day 1 predose; and predose and 2, 4, 6, and 8 hours postdose on Day 28. One patient, who received 150 mg abemaciclib, had a QTcF greater than 450 and an increase from baseline greater than 30 msec. There were no QTc intervals greater than 480 msec or QTcF change greater than 60 msec from baseline (Table APP.2.7.4.54).

Review of available safety data did not provide evidence of a clinically significant change in QT/QTcF, cardiac-related AEs, or abnormal electrolyte values. Additionally, there was no indication of QT prolongation with increased plasma abemaciclib or its active metabolite concentrations (M2 and M20) (Summary of Clinical Pharmacology Appendix, Section 2.7.2.5.5.3 JPBC).

### **MONARCH 1 (JPBN)**

In Study JPBN, patients received abemaciclib 200 mg orally every 12 ( $\pm$  2) hours on Days 1 to 28 of a 28-day cycle. During the study, 12-lead ECGs were collected in triplicate at the following times:

Baseline

Cycle 1 (4-6 hours after dosing on Day 1 and upon arrival at the site on Day 15)

Cycle 2 (3  $\pm$  0.5 hours postdose on Day 1)

Remaining Cycles (Day 1)

Overall, there were no consistent changes from baseline observed across all cycles and at follow-up. When analyzed by maximum postbaseline QTcF value, 46 patients (35.7%) had a QTcF change from baseline  $>30$  msec and no patients had a change  $>60$  msec (Table 2.7.4.33). Two patients had an absolute maximum postbaseline QTcF  $>500$  msec. One of these patients with a medical history of atrioventricular block second degree and left-ventricular dysfunction had an increase  $>30$  msec (this patient discontinued from treatment due to a Grade 2 TEAE of ECG QT prolonged possibly related to abemaciclib), and 1 patient with a preexisting condition of atrial fibrillation had an increase  $>30$  msec on Day 15 of Cycle 1 (this patient discontinued from treatment due to noncompliance with study drug).

There were no deaths due to cardiac disorders or selected non-cardiac disorders (syncope, seizure, or hypokalemia) during the study. Review of SAE data possibly related to

abemaciclib treatment revealed 1 SAE of hypokalemia (CTCAE Grade 3) and 1 patient that experienced sinus tachycardia (CTCAE Grade 3), both of which resolved.

The ECG data from MONARCH 1 did not reveal any clinically meaningful effects of abemaciclib on prolongation of QT/QTc interval. Additionally, there was no indication of QT prolongation with increased plasma abemaciclib or its active metabolite concentrations (M2 and M20) (Summary of Clinical Pharmacology Appendix, Section 2.7.2.5.5.4 JPBN).

**Table 2.7.4.33. Frequency Table of Maximum Postbaseline QTcF Value by Change in QTcF from Baseline Enrolled Population MONARCH 1**

| Maximum Postbaseline QTcF | Change in QTcF from Baseline | Abemaciclib 200 mg<br>N=132 <sup>a</sup><br>n (%) |
|---------------------------|------------------------------|---------------------------------------------------|
| Any                       | >30 ms                       | 46 (35.7)                                         |
| Any                       | >60 ms                       | 0 (0)                                             |
| >450 ms                   | Any                          | 24 (18.6)                                         |
| >450 ms                   | >30 ms                       | 18 (14.0)                                         |
| >450 ms                   | >60 ms                       | 0 (0)                                             |
| >480 ms                   | Any                          | 3 (2.3)                                           |
| >480 ms                   | >30 ms                       | 3 (2.3)                                           |
| >480 ms                   | >60 ms                       | 0 (0)                                             |
| >500 ms                   | Any                          | 2 (1.6)                                           |
| >500 ms                   | >30 ms                       | 2 (1.6)                                           |
| >500 ms                   | >60 ms                       | 0 (0)                                             |

Abbreviations: N = number of patients in the population who had non-missing values at baseline and at least 1 postbaseline visit; n = number of patients in the specified category; QTcF = QT interval corrected by Fridericia formula.

a 129 patients had a baseline and post-baseline value in QTcF; this value is used as the denominator for percentage calculation.

Source: frqtcfch.

### **Lilly Safety System Database SAE Review**

A cumulative search with a data cut-off of 30 April 2016 was conducted in LSS database using MedDRA Version 19.0 Standardized MedDRA query (SMQ) Arrhythmia related investigations, signs and symptoms (SMQ 20000051) and Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) (SMQ 20000050) to identify all cases suggestive of arrhythmia in healthy subjects and patients treated with abemaciclib in the following 11 clinical studies: JPBA, JPBB, JPBC, JPBD, JPBE, JPBF, JPBG, MONARCH 1 (JPBN), and JPBS, JPBU and JPBV.

A total of 10 cases were retrieved from Studies JPBA, JPBE and Monarch 1; there were no cases retrieved from Studies JPBB, JPBC, JPBD, JPBF, JPBG, JPBS, JPBU and JPBV (Table 2.7.4.34). Seven of the cases were female patients and 3 were male patients with an age range from 44 to 76 years. Nine cases were reported from the United States, and one case was reported from France.

**Table 2.7.4.34. Lilly Safety System Database SAE Review of Cardiac-Related Serious Adverse Events**

| Study | Patient | MedDRA Preferred Term      |
|-------|---------|----------------------------|
| JPBA  | 3051    | Syncope                    |
| JPBA  | 1032    | Sinus tachycardia          |
| JPBE  | 1015    | Sinus tachycardia          |
| JPBE  | 1016    | Syncope                    |
| JPBE  | 1034    | Atrial fibrillation        |
| JPBE  | 1026    | Atrial fibrillation        |
| JPBF  | 0123    | Syncope                    |
| JPBN  | 1039    | Electrocardiogram abnormal |
| JPBN  | 1161    | Tachycardia                |
| JPBN  | 1117    | Sinus bradycardia          |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Upon review, 8 of the 10 cases were assessed as unrelated to abemaciclib therapy by the investigator and the Sponsor and are not discussed here. Of the 2 remaining cases, Patient 1039, in Study JPBN, reported ECG abnormal and Subject 0123, Study JPBF, reported Syncope), the event of ECG abnormal is briefly described here and the event of syncope is described in Section 2.7.4E.3.3. Full narratives for both cases may be found in Module 5.3.5.3, TOSNP.

The ECG abnormal event was indirectly related to study drug per the investigator. In this case, the patient had a potassium level toward the lower limit of the normal range (3.6 mmol/L; normal range: 3.4 to 4.5) that was reported as hypokalemia by the investigator and Grade 2 diarrhea on the same day as the ECG abnormality. The patient received hydration and the event recovered. Sponsor's opinion was that there was insufficient evidence to attribute the ECG abnormality to abemaciclib, as the patient was receiving concomitant medications that may be associated with ECG changes. The event did not reoccur with study drug dose reduction.

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Abemaciclib's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND106100 (DARRTs [9/16/2015](#)). During the protocol review it was noted that the proposed dosing did not provide adequate exposure coverage to permit waiving the requirement for assay sensitivity and that the study would not support excluding small mean increases in the QTc interval (i.e. 10 ms).

The sponsor submitted the study report JPCA Clinical Pharmacology Study Report for abemaciclib, including electronic datasets and waveforms to the ECG warehouse.

### 4.2 QT STUDY

#### 4.2.1 Title

A Randomized, Single-Blind, Placebo-Controlled, Single Ascending Dose Study to Determine the Exposure-Response Relationship between Abemaciclib and QT Interval in Healthy Subjects.

#### 4.2.2 Protocol Number

Study I3Y-MC-JPCA

#### 4.2.3 Study Dates

Date of first enrolled (signed informed consent): 10 February 2016

Date of last subject completed (follow-up): 12 July 2016

#### 4.2.4 Objectives

**Primary objective:** To determine the relationship between plasma concentrations of abemaciclib and metabolites LSN2839567 (M2) and LSN3106726 (M20) and QT interval following single ascending oral doses of abemaciclib.

**Secondary objectives:**

- To evaluate the safety and tolerability of single ascending doses of abemaciclib in healthy volunteers
- To evaluate the pharmacokinetics (PK) of single ascending doses of abemaciclib in healthy volunteers
- To evaluate the effect of abemaciclib on the PK of loperamide, a P-glycoprotein (P-gp) substrate

**Exploratory objectives:**

- To evaluate the effect of loperamide on the PK of abemaciclib
- To assess the effect of abemaciclib on markers of renal function, including creatinine, cystatin C, kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL)

#### 4.2.5 Study Description

##### 4.2.5.1 Design

This single-blind, randomized, placebo-controlled, single ascending dose crossover study included 2 cohorts. For each cohort, a screening examination was conducted up to 28 days prior to enrollment to ensure eligibility for the study.

##### 4.2.5.2 Controls

The study utilized a negative (placebo) but not a positive (moxifloxacin) control.

##### 4.2.5.3 Blinding

Matching placebo capsules (Lot number CT595302) were supplied by Eli Lilly and Company. To maintain subject blinding in each period, subjects assigned to each sequence received the same number of capsules. Placebo capsules matched abemaciclib capsules in size and appearance.

#### 4.2.6 Treatment Regimen

##### 4.2.6.1 Treatment Arms

Cohort 1 was designed to evaluate the relationship between QT interval and exposure after oral administration of single ascending doses of 200, 300, and 400 mg of abemaciclib. Subjects in Cohort 1 were randomized to 1 of 4 sequences (1:1:1:1 ratio)

and received study drug as a single oral dose on Day 1 of each of 4 separate, consecutive periods (Periods 1, 2, 3, and 4) according to the randomization sequence. A washout of at least 5 days was required between doses.

| Period (Day)     | Sequence(s)   | Dose                 | Number of Capsules |         |
|------------------|---------------|----------------------|--------------------|---------|
|                  |               |                      | Abemaciclib*       | Placebo |
| Period 1 (Day 1) | SEQ 1         | Placebo              | 0                  | 2       |
|                  | SEQ 2, 3, & 4 | Abemaciclib (200 mg) | 2                  | 0       |
| Period 2 (Day 1) | SEQ 1         | Abemaciclib (200 mg) | 2                  | 1       |
|                  | SEQ 2         | Placebo              | 0                  | 3       |
|                  | SEQ 3 & 4     | Abemaciclib (300 mg) | 3                  | 0       |
| Period 3 (Day 1) | SEQ 1 & 2     | Abemaciclib (300 mg) | 3                  | 1       |
|                  | SEQ 3         | Placebo              | 0                  | 4       |
|                  | SEQ 4         | Abemaciclib (400 mg) | 4                  | 0       |
| Period 4 (Day 1) | SEQ 1, 2, & 3 | Abemaciclib (400 mg) | 4                  | 0       |
|                  | SEQ 4         | Placebo              | 0                  | 4       |

Abbreviations: SEQ = sequence.

Abemaciclib capsules 100-mg strength (C3)

Subjects were admitted to the clinical research unit (CRU) on Day -1 of each period. On Day 1, approximately 2 hours before study drug administration, subjects began continuous 12-lead digital Holter monitoring which continued until 24 hours postdose. Safety and tolerability assessments were performed for vital signs, clinical laboratory tests, markers of renal function, 12-lead electrocardiograms (ECGs), physical examinations, and adverse events (AEs). Blood samples were collected for the measurement of plasma concentrations of abemaciclib, M2, and M20 during the 24-hour Holter monitoring period (Days 1 and 2). Subjects were discharged from the CRU following safety assessments and PK sampling on Day 3 (48 hours after dosing), and returned to the CRU for safety assessments and/or PK sampling on Days 4, 5, and 6 of the period. Subjects returned for a follow-up assessment approximately 21 days after administration of their final dose of study drug.

## Cohort 2

Cohort 2 was designed to evaluate the drug-drug interaction between abemaciclib and the P-gp substrate loperamide, as well as dose escalation and QT interval relationship after oral administration of single ascending doses of abemaciclib. Subjects in Cohort 2 were randomized to 1 of 3 sequences (2:1:1 ratio) to receive study drug as a single oral dose on Day 1 of separate, consecutive periods according to the sequence to which they were randomized. A washout of at least 8 days was required between doses.

| Period (Day)      | Sequence(s)   | Dose                            | Number of Capsules |              |         |
|-------------------|---------------|---------------------------------|--------------------|--------------|---------|
|                   |               |                                 | LOP                | Abemaciclib* | Placebo |
| Period 4 (Day -3) | SEQ 1, 2, & 3 | LOP (8 mg)                      | 4                  | 0            | 0       |
| (Day 1)           | SEQ 1         | LOP (8 mg)+Placebo              | 4                  | 0            | 4       |
|                   | SEQ 2 & 3     | LOP (8 mg)+Abemaciclib (400 mg) | 4                  | 4            | 0       |
| Period 5 (Day 1)  | SEQ 1         | Placebo                         | NA                 | 0            | 4       |
|                   | SEQ 2 & 3     | Abemaciclib (400 mg)            | NA                 | 4            | 0       |
| Period 6 (Day 1)  | SEQ 1         | Abemaciclib (400 mg)            | NA                 | 4            | 2       |
|                   | SEQ 2         | Placebo                         | NA                 | 0            | 6       |
|                   | SEQ 3         | Abemaciclib (600 mg)            | NA                 | 6            | 0       |
| Period 7 (Day 1)  | SEQ 1 & 2     | Abemaciclib (600 mg)            | NA                 | 6            | 0       |
|                   | SEQ 3         | Placebo                         | NA                 | 0            | 6       |
| Period 8 (Day 1)  | SEQ 1, 2, & 3 | Abemaciclib (900 mg)            | NA                 | 9            | 0       |

Abbreviations: LOP = loperamide; NA = not applicable; SEQ = sequence.

\*Abemaciclib capsules 100-mg strength (C3)

#### ***Period 4 (DDI Assessment):***

Subjects in Cohort 2 started the study by participating in the DDI assessment during Period 4. Subjects were blinded to study dose (with the exception of loperamide, which was administered open-label). Subjects were admitted to the CRU on Day -4 of Period 4. On Day -3, subjects received a single oral 8-mg open-label dose of loperamide. Blood samples were collected for the measurement of plasma concentrations of loperamide and its metabolite, N-desmethyloperamide, on Day -3 to Day -1. On Day 1, subjects began approximately 2 hours of continuous 12-lead digital Holter monitoring before receiving a single oral 8-mg open-label dose of loperamide coadministered with a single oral 400-mg dose of abemaciclib or placebo. Safety and tolerability assessments were performed for vital signs, clinical laboratory tests, markers of renal function, 12-lead ECGs, physical examinations, and AEs. Blood samples were collected for the measurement of plasma concentrations of loperamide, N-desmethyloperamide, and abemaciclib, M2, and M20 during the 24-hour Holter monitoring period (Days 1 and 2), prior to discharge from the CRU on Day 3 (48 hours postdose), and on Day 4 (72 hours postdose). Blood sample collection continued for the measurement of plasma concentrations of abemaciclib, M2, and M20 on Days 5, 6, 7, 8, and 9. Blood and urine samples were collected for assessment of markers of renal function on Days 4 and 9.

#### ***Periods 5, 6, 7, and 8:***

While admitted in the CRU during Periods 5, 6, 7, and 8, subjects in Cohort 2 underwent the same procedures as described for subjects in Cohort 1, and were discharged following safety assessments and PK sampling on Day 3 (48 hours after dosing). Subjects returned to the CRU for PK sampling on Days 4, 5, 6, 7, 8, and 9, and collection of blood and urine samples for the assessment of markers of renal function on Days 4 and 9. Subjects returned to the CRU for a follow-up assessment approximately 21 days after administration of their final dose of study drug.

#### **4.2.6.2 Sponsor's Justification for Doses**

Prior to the conduct of this study, 275 mg abemaciclib (administered every 12 hours) was the highest dose that had been administered in patients (due to fatigue and nausea as dose-limiting toxicities [DLTs]), and the highest therapeutic dose and regimen of abemaciclib planned to be administered to cancer patients was 400 mg/day (200 mg

administered every 12 hours). Additionally, clinical study data evaluating a drug interaction with clarithromycin demonstrated that coadministration of abemaciclib with strong cytochrome P450 (CYP)3A inhibitors would produce the highest clinical exposures for abemaciclib. Therefore, a dose escalation ranging from 200 mg to 900 mg was selected for this study, if tolerated by study subjects, to encompass exposures that would be achieved at steady state with a dose of 200 mg every 12 hours as well as those that would be achieved in the setting of a worst-case drug interaction with a CYP3A inhibitor.

*Reviewer's Comment: The doses studied are unlikely to be sufficient to exclude small mean increases in the QTc interval (see section 4.1). However, given that the indication sought is an oncology indication, it is acceptable to exclude large mean increases in the QTc interval (i.e. 20 ms), which could be demonstrated by an upper bound of less than 10 ms at the expected therapeutic exposures (i.e. steady state  $C_{max}$ ).*

#### **4.2.6.3 Instructions with Regard to Meals**

Study drug capsules were administered with approximately 8 ounces (240 mL) of water. Food was restricted until at least 4 hours after dosing, at which time subjects were given a meal. Water was restricted from 1 hour before and 1 hour after dosing. Otherwise, subjects were allowed water as desired and meals were provided as appropriate at all other times.

*Reviewer's Comment: Acceptable. The effect of food on abemaciclib PK does not result in clinically relevant increases in exposure (AUC: 1.13,  $C_{max}$ : 1.30) per Appendix 6.1.*

#### **4.2.6.4 ECG and PK Assessments**

##### **Pharmacodynamic**

For the purposes of QT measurement for the primary analysis, continuous ECG monitoring was conducted for each subject using a 12-lead digital Holter recorder from approximately 2 hours predose through 24 hours postdose on Day 1 of each period. Up to ten 14-second 12-lead ECGs were extracted from the continuous Holter recording by the ECG laboratory at -2, -1.5, -1, -0.5, and -0.25 hours prior to dosing, and at 2, 4, 6, 8, 10, 12, 14, and 24 hours after dosing using the laboratory's thorough QT Plus ECG extraction method.

##### **Pharmacokinetic Analyses**

Venous blood samples were collected from subjects in Cohort 1(all periods) and Cohort 2 (Periods 5, 6, and 7) to determine the plasma concentrations of abemaciclib, M2, and M20 at the following times relative to dosing on Day 1 of each period: predose (-0.25 hour), and 2, 4, 6, 8, 10, 12, 14, 24, 48, 72, 96, and 120 hours postdose. Subjects in Cohort 2 continued to undergo blood sample collections at 144, 168, and 192 hours postdose.

*Reviewer's Comment: Acceptable. The timing of ECG/PK sampling is appropriate to capture potential QTc effects at  $T_{max}$  (for parent drug and major metabolites) and detect delayed effects over 24 hours.*

#### **4.2.6.5 Baseline**

The average of QTcF across all predose time points (including all replicates) on Day 1 (-2.0h, -1.5h, -1.0h, -0.5h, -0.25h) was calculated for each subject for each study period (Periods 1, 2, 3, 4, 5, 6 and 7) as the period-specific baseline. The study periods of Cohort 1 subjects were Periods 1, 2, 3 and 4, and those of Cohort 2 subjects Periods 4, 5, 6 and 7.

#### **4.2.7 ECG Collection**

Continuous 12-Lead digital Holter ECG extraction was performed from the 2-hour predose timepoint (-2.0h) through the 24-hour postdose timepoint (24h).

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A total of 35 subjects entered the study; 20 subjects in Cohort 1 and 15 subjects in Cohort 2 were randomly assigned to study sequences and received at least 1 dose of study drug. A total of 34 subjects completed the study; 19 subjects in Cohort 1 completed Periods 1 through 4. All of the subjects in Cohort 2 completed Periods 4 through 7, and the study was not continued on to Period 8 based on safety review. The discontinuation from Cohort 1 was due to family emergency.

##### **4.2.8.2 Statistical Analyses**

###### ***4.2.8.2.1 Primary Analysis***

The exposure-response analysis was used for primary analysis. The findings of the studies are discussed in section 4.2.8.4.2.

###### ***4.2.8.2.2 Assay Sensitivity***

Assay sensitivity was not assessed in the submitted study.

###### ***4.2.8.2.3 Categorical Analysis***

The Sponsor provides their categorical analysis results in the following table.

**Table 1: Categorical Analysis of QTc Interval Data. (Sponsor's Table JPCA.7.2)**

| Dose                      | QTcF interval (msec) |          |          | Maximum increase in QTcF interval (msec) <sup>a</sup> |          | PR (msec) | QRS (msec) |
|---------------------------|----------------------|----------|----------|-------------------------------------------------------|----------|-----------|------------|
|                           | >450                 | >480     | >500     | >30                                                   | >60      | >200      | >110       |
|                           | n (%)                | n (%)    | n (%)    | n (%)                                                 | n (%)    | n (%)     | n (%)      |
| Placebo (N=34)            | 0 (0.0%)             | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)                                              | 0 (0.0%) | 0 (0.0%)  | 0 (0.0%)   |
| Abemaciclib 200 mg (N=20) | 0 (0.0%)             | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)                                              | 0 (0.0%) | 0 (0.0%)  | 0 (0.0%)   |
| Abemaciclib 300 mg (N=20) | 0 (0.0%)             | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)                                              | 0 (0.0%) | 0 (0.0%)  | 0 (0.0%)   |
| Abemaciclib 400 mg (N=35) | 2 (5.7%)             | 0 (0.0%) | 0 (0.0%) | 0 (0.0%)                                              | 0 (0.0%) | 0 (0.0%)  | 0 (0.0%)   |
| Abemaciclib 600 mg (N=15) | 1 (6.7%)             | 0 (0.0%) | 0 (0.0%) | 1 (6.7%)                                              | 0 (0.0%) | 1 (6.7%)  | 0 (0.0%)   |

n = Number of subjects; N = Number of subjects studied

<sup>a</sup> Baseline is defined as the mean of the predose measurements.

#### 4.2.8.3 Safety Analysis

There were no deaths or other SAEs.

Drug-related AE experienced by more than one subject was nausea or diarrhea after an administration of 200 mg and 300 mg, and diarrhea, nausea, headache, vomiting, abdominal pain, and dyspepsia after an administration of 400 mg and 600 mg.

Because both the frequency of mild gastrointestinal events had increased upon 600 mg dose administration and 3 subjects had moderate events of diarrhea which the investigator determined had significantly interfered with daily activities, the Safety Review Panel deemed these tolerability issues met the protocol-specified criteria limiting further dose escalation. Thus, Period 8 was not completed and no subjects were administered a 900 mg dose. The Sponsor determined Abemaciclib 400 mg as the maximum tolerated dose (MTD) in this study.

## 4.2.8.4 Clinical Pharmacology

### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 2 (Abemaciclib).  $C_{max}$  and AUC values in the thorough QT study were similar following administration of 600 mg ( $C_{max}$  for abemaciclib 308 ng/mL; 45% CV) Drug Supra compared with 200 mg Q12H drug (298 ng/mL; 72% CV), the intended clinical dose.

Coadministration of abemaciclib with loperamide resulted in increased systemic exposure of loperamide and its metabolite N-desmethylloperamide; however, these increases were not considered clinically significant. Loperamide did not significantly affect the PK of abemaciclib. Collectively, these data suggest that abemaciclib can be safely coadministered with loperamide.

**Table 2: Summary of Plasma Abemaciclib Pharmacokinetic Parameters Following Oral Administration of Abemaciclib in Healthy Subjects (Sponsor's Table JPCA.7.6)**

| PK Parameters                     | Geometric Mean (CV%) |                     |                                 |                       |                                           |
|-----------------------------------|----------------------|---------------------|---------------------------------|-----------------------|-------------------------------------------|
|                                   | Abemaciclib 200 mg   | Abemaciclib 300 mg  | Abemaciclib 400 mg <sup>c</sup> | Abemaciclib 600 mg    | Abemaciclib 400 mg with Loperamide (8 mg) |
| N                                 | 19                   | 20                  | 31                              | 8                     | 7                                         |
| AUC(0- $t_{last}$ ) (ng•hr/mL)    | 3560 (38)            | 5210 (37)           | 7610 (46)                       | 14600 (42)            | 9420 (57)                                 |
| AUC(0- $\infty$ ) (ng•hr/mL)      | 3680 (38)            | 5420 (40)           | 7840 (47)                       | 14800 (42)            | 9520 (57)                                 |
| %AUC( $t_{last}$ - $\infty$ ) (%) | 2.68 (72)            | 2.99 (91)           | 1.96 (108)                      | 0.887 (80)            | 0.830 (72)                                |
| $C_{max}$ (ng/mL)                 | 102 (31)             | 130 (40)            | 182 (42)                        | 308 (45)              | 199 (55)                                  |
| $t_{max}$ <sup>a</sup> (hr)       | 8.23 (6.10 – 14.10)  | 8.10 (6.10 – 24.10) | 10.05 (6.05 – 24.13)            | 10.08 (10.05 – 14.07) | 10.07 (6.05 – 12.07)                      |
| $t_{1/2}$ <sup>b</sup> (hr)       | 21.6 (14.2 – 30.0)   | 22.6 (12.7 – 32.9)  | 25.0 (14.8 – 36.6)              | 27.6 (23.3 – 33.8)    | 26.5 (21.9 – 30.6)                        |
| CL/F (L/hr)                       | 54.4 (38)            | 55.3 (40)           | 51.0 (47)                       | 40.6 (42)             | 42.0 (57)                                 |
| $V_z$ /F (L)                      | 1700 (31)            | 1800 (28)           | 1840 (40)                       | 1610 (47)             | 1610 (58)                                 |
| $V_{ss}$ /F (L)                   | 1930 (33)            | 2140 (33)           | 2120 (41)                       | 1840 (48)             | 1870 (60)                                 |

Abbreviations: AUC(0- $\infty$ ) = area under the concentration versus time curve from time zero to infinity; AUC(0- $t_{last}$ ) = area under the concentration versus time curve from time zero to time  $t$ , where  $t$  is the last time point with a measurable concentration; %AUC( $t_{last}$ - $\infty$ ) = percentage of AUC(0- $\infty$ ) extrapolated; CL/F = apparent total body clearance of drug at steady state calculated after oral administration;  $C_{max}$  = maximum observed drug concentration; CV = coefficient of variation; N = number of subjects;  $t_{1/2}$  = half-life associated with the terminal rate constant ( $\lambda_z$ ) in non-compartmental analysis;  $t_{max}$  = time of maximum observed drug concentration;  $V_z$ /F = apparent volume of distribution at steady state after oral administration;  $V_{ss}$ /F = apparent volume of distribution during the terminal phase after oral administration.

<sup>a</sup> Median (range).

<sup>b</sup> Geometric mean (range).

<sup>c</sup> Includes both Cohort 1, Period 4 and Cohort 2, Period 5 400-mg abemaciclib data.

**Table 3: Summary of Plasma M2 Pharmacokinetic Parameters Following Oral Administration of Abemaciclib in Healthy Subjects (Sponsor's Table JPCA.7.7)**

| PK Parameters                        | Geometric Mean (CV%) |                     |                                 |                      |                                           |
|--------------------------------------|----------------------|---------------------|---------------------------------|----------------------|-------------------------------------------|
|                                      | Abemaciclib 200 mg   | Abemaciclib 300 mg  | Abemaciclib 400 mg <sup>c</sup> | Abemaciclib 600 mg   | Abemaciclib 400 mg with Loperamide (8 mg) |
| N                                    | 19                   | 13                  | 22                              | 8                    | 7                                         |
| AUC(0-t <sub>last</sub> ) (ng•hr/mL) | 1190 (21)            | 2080 (24)           | 2810 (46)                       | 5210 (42)            | 3320 (53)                                 |
| AUC(0-∞) (ng•hr/mL)                  | 1460 (19)            | 2490 (24)           | 3170 (45)                       | 5650 (42)            | 3610 (51)                                 |
| %AUC(t <sub>last</sub> -∞) (%)       | 17.2 (35)            | 15.6 (28)           | 11.0 (30)                       | 7.17 (41)            | 7.50 (45)                                 |
| C <sub>max</sub> (ng/mL)             | 28.1 (27)            | 48.1 (40)           | 58.2 (48)                       | 96.0 (37)            | 67.2 (46)                                 |
| t <sub>max</sub> <sup>a</sup> (hr)   | 6.10 (4.10 – 24.10)  | 8.10 (4.13 – 14.10) | 8.09 (4.05 – 14.10)             | 10.05 (6.05 – 14.07) | 10.05 (6.05 – 12.07)                      |
| t <sub>1/2</sub> <sup>b</sup> (hr)   | 49.4 (35.6 – 91.4)   | 46.7 (36.5 – 60.1)  | 52.0 (33.2 – 77.9)              | 53.0 (41.4 – 64.5)   | 54.5 (43.1 – 64.4)                        |
| MR                                   | 0.419 (29)           | 0.485 (33)          | 0.439 (33)                      | 0.404 (19)           | 0.402 (18)                                |

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t<sub>last</sub>) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; %AUC(t<sub>last</sub>-∞) = percentage of AUC(0-∞) extrapolated; C<sub>max</sub> = maximum observed drug concentration; CV = coefficient of variation; MR = metabolic ratio; N = number of subjects; t<sub>1/2</sub> = half-life associated with the terminal rate constant (λ<sub>z</sub>) in non-compartmental analysis; t<sub>max</sub> = time of maximum observed drug concentration.

<sup>a</sup> Median (range).

<sup>b</sup> Geometric mean (range).

<sup>c</sup> Includes both Cohort 1 and Cohort 2 400-mg abemaciclib data.

**Table 4: Summary of Plasma M20 Pharmacokinetic Parameters Following Oral Administration of Abemaciclib in Healthy Subjects (Sponsor's Table JPCA.7.8)**

| PK Parameters                        | Geometric Mean (CV%) |                      |                                 |                       |                                           |
|--------------------------------------|----------------------|----------------------|---------------------------------|-----------------------|-------------------------------------------|
|                                      | Abemaciclib 200 mg   | Abemaciclib 300 mg   | Abemaciclib 400 mg <sup>c</sup> | Abemaciclib 600 mg    | Abemaciclib 400 mg with Loperamide (8 mg) |
| N                                    | 19                   | 17                   | 26                              | 8                     | 7                                         |
| AUC(0-t <sub>last</sub> ) (ng•hr/mL) | 2860 (20)            | 4140 (24)            | 5430 (40)                       | 10100 (38)            | 6430 (54)                                 |
| AUC(0-∞) (ng•hr/mL)                  | 3130 (21)            | 4590 (25)            | 5790 (41)                       | 10400 (38)            | 6610 (55)                                 |
| %AUC(t <sub>last</sub> -∞) (%)       | 7.59 (62)            | 8.33 (65)            | 4.73 (85)                       | 2.96 (60)             | 2.28 (71)                                 |
| C <sub>max</sub> (ng/mL)             | 52.1 (24)            | 70.3 (35)            | 83.1 (41)                       | 132 (40)              | 89.6 (55)                                 |
| t <sub>max</sub> <sup>a</sup> (hr)   | 9.17 (6.10 – 24.18)  | 12.10 (4.10 – 24.12) | 11.10 (6.05 – 48.00)            | 24.05 (10.05 – 24.25) | 12.08 (6.05 – 48.00)                      |
| t <sub>1/2</sub> <sup>b</sup> (hr)   | 30.6 (20.5 – 43.3)   | 31.6 (20.2 – 52.2)   | 32.8 (18.1 – 48.0)              | 35.2 (30.1 – 48.0)    | 33.2 (26.7 – 45.3)                        |
| MR                                   | 0.826 (22)           | 0.852 (23)           | 0.772 (25)                      | 0.683 (21)            | 0.674 (15)                                |

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t<sub>last</sub>) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; %AUC(t<sub>last</sub>-∞) = percentage of AUC(0-∞) extrapolated; C<sub>max</sub> = maximum observed drug concentration; CV = coefficient of variation; MR = metabolic ratio; N = number of subjects; t<sub>1/2</sub> = half-life associated with the terminal rate constant (λ<sub>z</sub>) in non-compartmental analysis; t<sub>max</sub> = time of maximum observed drug concentration.

<sup>a</sup> Median (range).

<sup>b</sup> Geometric mean (range).

<sup>c</sup> Includes both Cohort 1 and Cohort 2 400-mg abemaciclib data.

#### 4.2.8.4.2 Exposure-Response Analysis

Exposure-response analysis was conducted by pairing ECG data collected during an intense ECG schedule and PK data in order to delineate effects of abemaciclib, M2, and M20 on QT interval.

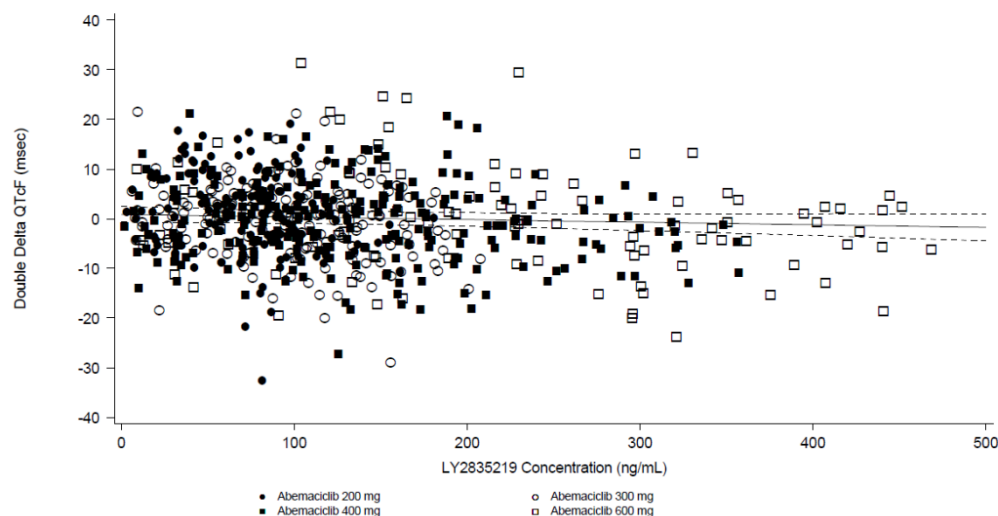
The relationship between plasma concentrations of abemaciclib and its major active metabolites and  $\Delta\Delta\text{QTcF}$  were evaluated using a linear mixed-effects model. The fitted slopes, the predicted mean  $\Delta\Delta\text{QTcF}$  at  $C_{\text{max}}$  for each dose, and their corresponding 90% CIs are presented in Table 5. The results show that the slopes of  $\Delta\Delta\text{QTcF}$  and abemaciclib, M2, M20, and total analyte concentrations are not statistically different from 0 (p-value >0.05). In addition, the upper bound of the 90% CI of the predicted  $\Delta\Delta\text{QTcF}$  does not cross the 10 msec threshold at the highest observed (Figure 1), M2 (Figure 2), M20 (Figure 3), and total analyte (Figure 4) concentrations.

**Table 5: Exposure-Response Analysis Results (Sponsor's Table JPCA.7.3.)**

|               | Fitted line |                  |         | Predicted mean placebo-adjusted change from baseline $\Delta\Delta\text{QTcF}$ at $C_{\text{max}}$ and its 2-sided 90% CI (msec) |                    |                     |                     |
|---------------|-------------|------------------|---------|----------------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------|---------------------|
|               | Slope       | 90% CI           | p-value | 200 mg                                                                                                                           | 300 mg             | 400 mg              | 600 mg              |
| Abemaciclib   | -0.005      | (-0.012, 0.001)  | 0.2017  | 0.36 (-0.95, 1.68)                                                                                                               | 0.21 (-1.08, 1.50) | -0.08 (-1.40, 1.24) | -0.63 (-2.27, 1.00) |
| M2            | -0.032      | (-0.056, -0.009) | 0.0252  | 0.64 (-0.68, 1.96)                                                                                                               | 0.33 (-0.95, 1.61) | -0.26 (-1.57, 1.05) | -1.33 (-3.00, 0.34) |
| M20           | -0.009      | (-0.025, 0.008)  | 0.3867  | 0.27 (-1.06, 1.60)                                                                                                               | 0.16 (-1.16, 1.47) | -0.01 (-1.36, 1.35) | -0.33 (-1.94, 1.28) |
| Total analyte | -0.002      | (-0.004, 0.000)  | 0.1612  | 0.40 (-0.92, 1.72)                                                                                                               | 0.22 (-1.07, 1.51) | -0.11 (-1.43, 1.22) | -0.70 (-2.34, 0.93) |

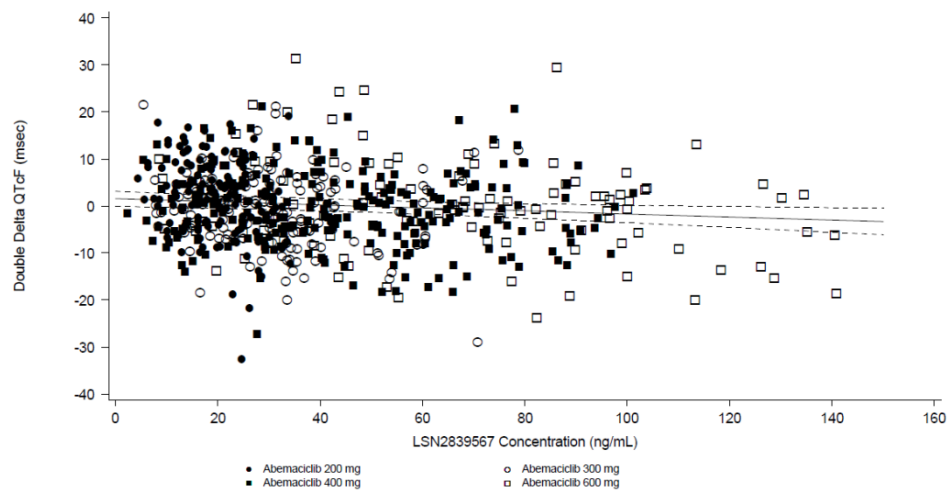
Abbreviations: CI = confidence interval

**Figure 1: QTcF changes from baseline and placebo versus abemaciclib plasma concentrations. (Sponsor's Figure JPCA.7.1.)**



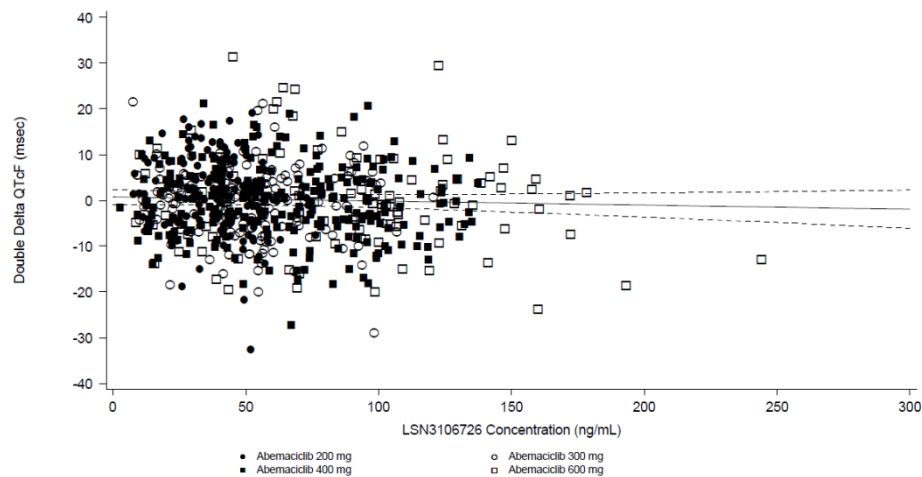
Double delta QTcF =  $0.86 - 0.005 \times \text{LY2835219 Conc} + \text{Subject}$ , where Subject is fitted as a random effect  
P-value for slope: 0.2017, 90% CI for slope: (-0.012, 0.001)  
Double delta change (90% CI) at  $C_{\text{max}}$  at dose: 200 mg = 0.36 (-0.95, 1.68);  
300 mg = 0.21 (-1.08, 1.50); 400 mg = -0.08 (-1.40, 1.24); 600 mg = -0.63 (-2.27, 1.00).  
Dashed lines represent the 90% confidence intervals  
Double delta changes are based on an individual subjects baseline and placebo data  
Baseline is defined as the mean of the predose measurements  
BLQ plasma concentrations were set to missing

**Figure 2: QTcF changes from baseline and placebo versus M2 (LSN2839567) plasma concentrations (Sponsor's Figure JPCA.7.2.)**



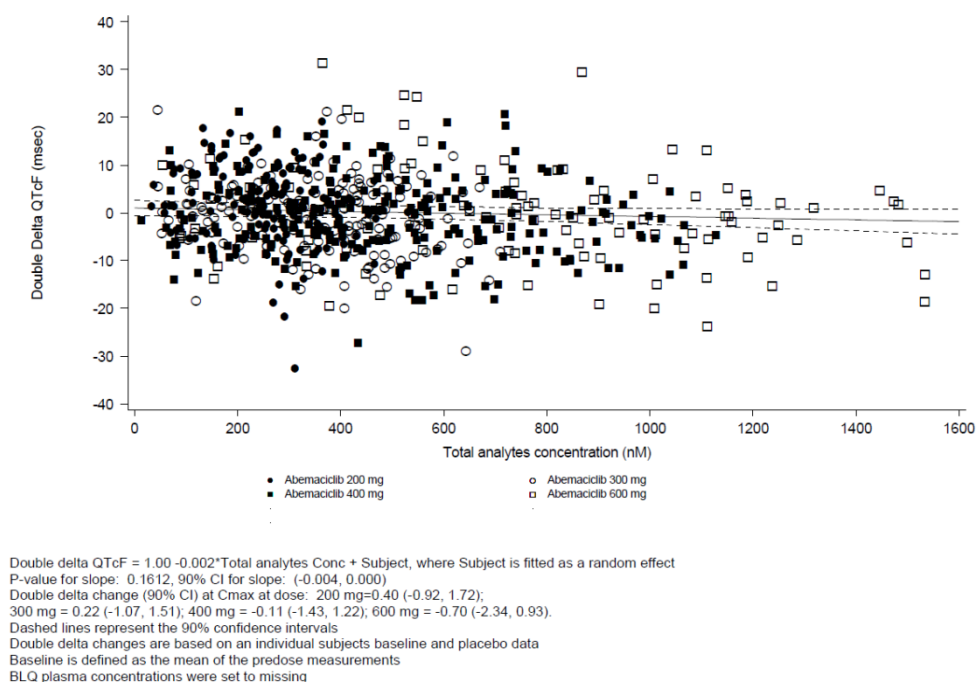
Double delta QTcF =  $1.51 - 0.032 \cdot \text{LSN2839567 Conc} + \text{Subject}$ , where Subject is fitted as a random effect  
P-value for slope: 0.0252, 90% CI for slope: (-0.056, -0.009)  
Double delta change (90% CI) at Cmax at dose: 200 mg = 0.64 (-0.68, 1.96);  
300 mg = 0.33 (-0.95, 1.61); 400 mg = -0.26 (-1.57, 1.05); 600 mg = -1.33 (-3.00, 0.34).  
Dashed lines represent the 90% confidence intervals  
Double delta changes are based on an individual subjects baseline and placebo data  
Baseline is defined as the mean of the predose measurements  
BLQ plasma concentrations were set to missing

**Figure 3: QTcF changes from baseline and placebo versus M20 (LSN3106726) plasma concentrations (Sponsor's Figure JPCA.7.3.)**



Double delta QTcF =  $0.71 - 0.009 \cdot \text{LSN3106726 Conc} + \text{Subject}$ , where Subject is fitted as a random effect  
P-value for slope: 0.3867, 90% CI for slope: (-0.025, 0.008)  
Double delta change (90% CI) at Cmax at dose: 200 mg = 0.27 (-1.06, 1.60);  
300 mg = 0.16 (-1.16, 1.47); 400 mg = -0.01 (-1.36, 1.35); 600 mg = -0.33 (-1.94, 1.28).  
Dashed lines represent the 90% confidence intervals  
Double delta changes are based on an individual subjects baseline and placebo data  
Baseline is defined as the mean of the predose measurements  
BLQ plasma concentrations were set to missing

**Figure 4: QTcF changes from baseline and placebo versus total analyte plasma concentrations. (Sponsor's Figure JPCA.7.4.)**



*Reviewer's comment: Please see the reviewer's analysis in section 5.3.*

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

In all the subsequent analysis the QT interval was corrected for heart rate using Fridericia's correction (QTcF), which is in alignment with the primary analysis by the sponsor and is acceptable as no heart rate increases or decreases were observed (see sections 5.2.2 and 5.3).

### 5.2 STATISTICAL ASSESSMENTS

#### 5.2.1 QTc Analysis

##### 5.2.1.1 The Primary Analysis for Abemaciclib

The statistical reviewer used a repeated measure linear mixed model to analyze the  $\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcF}$  effect for both cohorts. Analysis was performed on each of the cohorts, separately. The model includes SEQUENCE, PERIOD, TREATMENT, TIME, and INTERACTION of TREATMENT and TIME as fixed effects and SUBJECT as a random effect. Baseline values are added to the model as a covariate. The interaction of baseline values and TIME is also included. The analysis results are listed in the following tables.

For Cohort 1, data from Periods 1, 2, 3 and 4 (Abemaciclib 200 mg, 300 mg, 400 mg, and Placebo) obtained per study design were used for an evaluation of QT prolongation.

As for Cohort 2, data from Period 5, 6 and 7 (Abemaciclib 400 mg, 600 mg and Placebo) were used for an evaluation of QT prolongation. The Period 4 data were not included because the objective of Period 4 of Cohort 2, in which subjects were exposed to loperamide, was to assess drug-drug interaction (Abemaciclib and Loperamide).

As shown in Table 6, Table 7 and Table 8, for Cohort 1, the largest upper bounds of the 2-sided 90% CI on  $\Delta\Delta\text{QTcF}$  for the mean difference between Abemaciclib 200 mg and placebo, between Abemaciclib 300 mg and placebo, and between Abemaciclib 400 mg and placebo were 10.2 ms, 5.7 ms and 5.7 ms, respectively. As shown in Table 9 and Table 10, for Cohort 2, the largest upper bounds of the 2-sided 90% CI for the mean difference between Abemaciclib 400 mg and placebo, and between Abemaciclib 600 mg and placebo were 7.9 ms and 12.2 ms, respectively.

**Table 6: Analysis Results of  $\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcF}$  Abemaciclib 200 mg (Cohort 1)**

| Time | $\Delta\text{QTcF}$ : Abemaciclib 200 mg |                                               | $\Delta\text{QTcF}$ : Placebo |                                               | $\Delta\Delta\text{QTcF}$                                                   |
|------|------------------------------------------|-----------------------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|      | N                                        | LS mean estimate<br>(90% Confidence Interval) | N                             | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of<br>Difference from Placebo<br>(90% Confidence Interval) |
| 2    | 19                                       | -0.6 (-3.5, 2.2)                              | 19                            | -3.4 (-5.8, -1.0)                             | 2.8 (-1.0, 6.5)                                                             |
| 4    | 20                                       | -0.4 (-3.2, 2.5)                              | 19                            | 0.6 (-1.9, 3.0)                               | -0.9 (-4.6, 2.8)                                                            |
| 6    | 19                                       | -1.5 (-4.4, 1.4)                              | 18                            | -4.4 (-6.9, -1.9)                             | 3.0 (-0.8, 6.8)                                                             |
| 8    | 19                                       | -5.2 (-8.1, -2.3)                             | 19                            | -9.7 (-12.2, -7.3)                            | 4.6 (0.8, 8.3)                                                              |
| 10   | 19                                       | -3.5 (-6.4, -0.6)                             | 19                            | -7.2 (-9.7, -4.8)                             | 3.7 (-0.1, 7.4)                                                             |
| 12   | 19                                       | -3.4 (-6.3, -0.5)                             | 19                            | -5.4 (-7.8, -2.9)                             | 2.0 (-1.8, 5.7)                                                             |
| 14   | 20                                       | 1.5 (-1.3, 4.4)                               | 20                            | -5.0 (-7.4, -2.6)                             | 6.5 (2.8, 10.2)                                                             |
| 24   | 19                                       | -0.1 (-3.0, 2.8)                              | 19                            | -3.6 (-6.0, -1.1)                             | 3.5 (-0.3, 7.2)                                                             |

**Table 7: Analysis Results of  $\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcF}$  Abemaciclib 300 mg (Cohort 1)**

| Time | $\Delta\text{QTcF}$ : Abemaciclib 300 mg |                                               | $\Delta\text{QTcF}$ : Placebo |                                               | $\Delta\Delta\text{QTcF}$                                                   |
|------|------------------------------------------|-----------------------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|      | N                                        | LS mean estimate<br>(90% Confidence Interval) | N                             | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of Difference<br>from Placebo<br>(90% Confidence Interval) |
| 2    | 20                                       | -2.2 (-4.8, 0.4)                              | 19                            | -3.4 (-5.8, -1.0)                             | 1.2 (-2.3, 4.8)                                                             |
| 4    | 19                                       | -1.6 (-4.2, 1.0)                              | 19                            | 0.6 (-1.9, 3.0)                               | -2.2 (-5.8, 1.4)                                                            |
| 6    | 19                                       | -5.8 (-8.4, -3.2)                             | 18                            | -4.4 (-6.9, -1.9)                             | -1.3 (-4.9, 2.3)                                                            |
| 8    | 20                                       | -9.5 (-12.0, -6.9)                            | 19                            | -9.7 (-12.2, -7.3)                            | 0.3 (-3.3, 3.8)                                                             |
| 10   | 20                                       | -8.0 (-10.6, -5.4)                            | 19                            | -7.2 (-9.7, -4.8)                             | -0.8 (-4.3, 2.8)                                                            |
| 12   | 20                                       | -8.7 (-11.3, -6.2)                            | 19                            | -5.4 (-7.8, -2.9)                             | -3.4 (-6.9, 0.1)                                                            |
| 14   | 21                                       | -4.3 (-6.8, -1.7)                             | 20                            | -5.0 (-7.4, -2.6)                             | 0.7 (-2.7, 4.2)                                                             |
| 24   | 19                                       | -1.5 (-4.1, 1.1)                              | 19                            | -3.6 (-6.0, -1.1)                             | 2.1 (-1.5, 5.7)                                                             |

**Table 8: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Abemaciclib 400 mg (Cohort 1)**

| Time | $\Delta$ QTcF: Abemaciclib 400 mg |                                            | $\Delta$ QTcF: Placebo |                                            | $\Delta\Delta$ QTcF                                                   |
|------|-----------------------------------|--------------------------------------------|------------------------|--------------------------------------------|-----------------------------------------------------------------------|
|      | N                                 | LS mean estimate (90% Confidence Interval) | N                      | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| 2    | 20                                | -1.7 (-4.6, 1.1)                           | 19                     | -3.4 (-5.8, -1.0)                          | 1.7 (-2.1, 5.4)                                                       |
| 4    | 20                                | -2.9 (-5.7, 0.0)                           | 19                     | 0.6 (-1.9, 3.0)                            | -3.4 (-7.2, 0.4)                                                      |
| 6    | 20                                | -6.9 (-9.8, -4.1)                          | 18                     | -4.4 (-6.9, -1.9)                          | -2.5 (-6.3, 1.3)                                                      |
| 8    | 19                                | -7.9 (-10.7, -5)                           | 19                     | -9.7 (-12.2, -7.3)                         | 1.9 (-1.9, 5.7)                                                       |
| 10   | 19                                | -8.7 (-11.6, -5.9)                         | 19                     | -7.2 (-9.7, -4.8)                          | -1.5 (-5.3, 2.3)                                                      |
| 12   | 19                                | -8.3 (-11.1, -5.4)                         | 19                     | -5.4 (-7.8, -2.9)                          | -2.9 (-6.7, 0.9)                                                      |
| 14   | 20                                | -4.4 (-7.3, -1.6)                          | 20                     | -5.0 (-7.4, -2.6)                          | 0.6 (-3.2, 4.4)                                                       |
| 24   | 20                                | -4.6 (-7.5, -1.8)                          | 19                     | -3.6 (-6, -1.1)                            | -1.1 (-4.8, 2.7)                                                      |

**Table 9: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF Abemaciclib 400 mg (Cohort 2)**

| Time | $\Delta$ QTcF: Abemaciclib 400 mg |                                            | $\Delta$ QTcF: Placebo |                                            | $\Delta\Delta$ QTcF                                                   |
|------|-----------------------------------|--------------------------------------------|------------------------|--------------------------------------------|-----------------------------------------------------------------------|
|      | N                                 | LS mean estimate (90% Confidence Interval) | N                      | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| 2    | 14                                | -10.1 (-14.3, -5.9)                        | 15                     | -2.4 (-6.2, 1.4)                           | -7.7 (-13.2, -2.2)                                                    |
| 4    | 14                                | -6.4 (-10.6, -2.2)                         | 15                     | -3.9 (-7.7, -0.1)                          | -2.5 (-8.1, 3.0)                                                      |
| 6    | 14                                | -11.8 (-16.1, -7.6)                        | 14                     | -6.5 (-10.4, -2.7)                         | -5.3 (-10.9, 0.3)                                                     |
| 8    | 14                                | -14.1 (-18.3, -9.8)                        | 14                     | -12.2 (-16.1, -8.3)                        | -1.8 (-7.5, 3.8)                                                      |
| 10   | 14                                | -9.4 (-13.6, -5.2)                         | 14                     | -11.6 (-15.5, -7.8)                        | 2.3 (-3.4, 7.9)                                                       |
| 12   | 14                                | -9.7 (-13.9, -5.5)                         | 15                     | -8.4 (-12.2, -4.6)                         | -1.3 (-6.8, 4.2)                                                      |
| 14   | 14                                | -7.8 (-12.0, -3.6)                         | 15                     | -6.5 (-10.3, -2.6)                         | -1.4 (-7.0, 4.3)                                                      |
| 24   | 14                                | -18.4 (-22.6, -14.2)                       | 13                     | -14.7 (-18.7, -10.7)                       | -3.7 (-9.4, 2.0)                                                      |

**Table 10: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF Abemaciclib 600 mg (Cohort 2)**

| Time | $\Delta$ QTcF: Abemaciclib 600 mg |                                            | $\Delta$ QTcF: Placebo |                                            | $\Delta\Delta$ QTcF                                                   |
|------|-----------------------------------|--------------------------------------------|------------------------|--------------------------------------------|-----------------------------------------------------------------------|
|      | N                                 | LS mean estimate (90% Confidence Interval) | N                      | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| 2    | 15                                | -4.8 (-9.0, -0.5)                          | 15                     | -2.4 (-6.2, 1.4)                           | -2.3 (-8.2, 3.5)                                                      |

| Time | $\Delta$ QTcF: Abemaciclib 600 mg |                                            | $\Delta$ QTcF: Placebo |                                            | $\Delta\Delta$ QTcF                                                   |
|------|-----------------------------------|--------------------------------------------|------------------------|--------------------------------------------|-----------------------------------------------------------------------|
|      | N                                 | LS mean estimate (90% Confidence Interval) | N                      | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| 4    | 15                                | -8 (-12.2, -3.7)                           | 15                     | -3.9 (-7.7, -0.1)                          | -4.0 (-9.9, 1.8)                                                      |
| 6    | 15                                | -10.5 (-14.8, -6.3)                        | 14                     | -6.5 (-10.4, -2.7)                         | -4.0 (-9.9, 1.9)                                                      |
| 8    | 15                                | -9.7 (-14, -5.5)                           | 14                     | -12.2 (-16.1, -8.3)                        | 2.5 (-3.4, 8.3)                                                       |
| 10   | 15                                | -5.3 (-9.6, -1.1)                          | 14                     | -11.6 (-15.5, -7.8)                        | 6.3 (0.5, 12.2)                                                       |
| 12   | 15                                | -3.4 (-7.7, 0.8)                           | 15                     | -8.4 (-12.2, -4.6)                         | 4.9 (-0.9, 10.8)                                                      |
| 14   | 15                                | -4.7 (-9.0, -0.5)                          | 15                     | -6.5 (-10.3, -2.6)                         | 1.7 (-4.1, 7.6)                                                       |
| 24   | 15                                | -14.2 (-18.4, -9.9)                        | 13                     | -14.7 (-18.7, -10.7)                       | 0.5 (-5.4, 6.5)                                                       |

It appears that Abemaciclib 200 mg had a relatively high largest upper bound at Hour 14. It is noted that an increase from baseline in QTcF was not observed at Hour 14 in subjects given Abemaciclib 200 mg, and that subjects given placebo had a relatively larger decrease from baseline in QTcF than Abemaciclib 200 mg subjects at almost every time point. This apparently caused the upper bounds of the 90% CI's for Abemaciclib 200 mg versus placebo to tend to have a relatively larger value.

For the large values of the largest upper bound of 90% CI's at Hours 10 and 12 in subjects administered Abemaciclib 600 mg, it is noted that subjects administered Abemaciclib 600 mg tended to have a decreased QTcF compared to their baseline values, and subjects given placebo had an even more decrease in QTcF. The reader is also referred to section 5.2.1.4.

### 5.2.1.2 Assay Sensitivity Analysis

Not applicable.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Time profile of  $\Delta\Delta$ QTcF for different treatment groups are displayed for each cohort in Figure 5 and Figure 6. Note that the CIs are all unadjusted.

**Figure 5: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse (Cohort 1)**

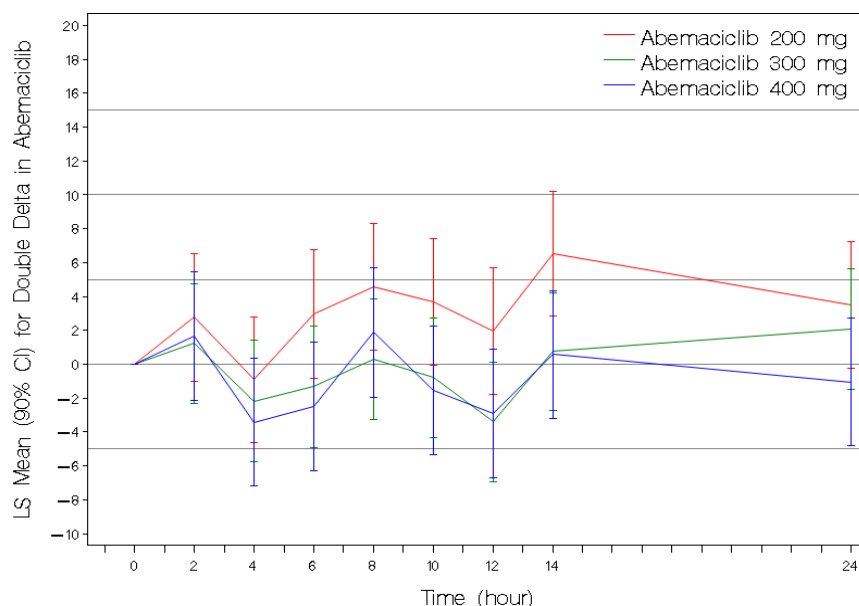
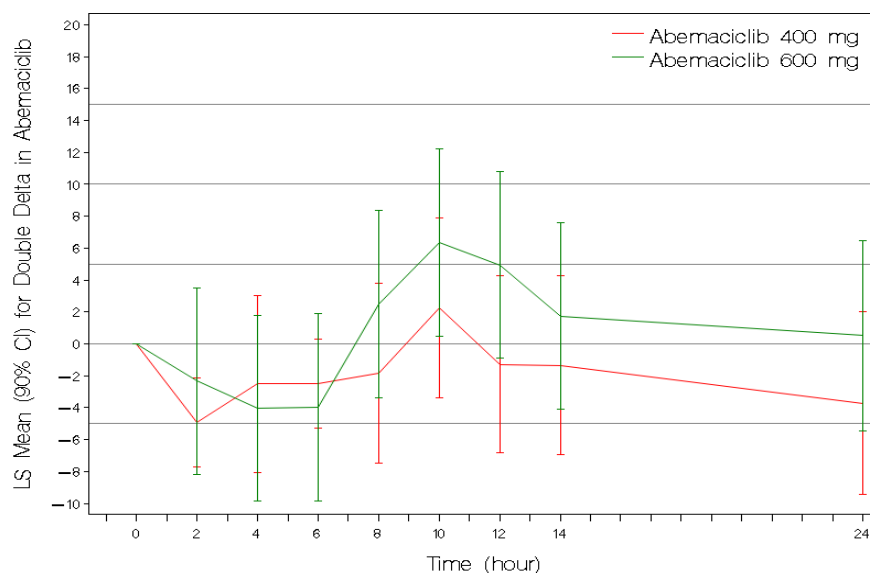


**Figure 6: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse (Cohort 2)**



#### 5.2.1.4 Additional Analysis

The upper bounds of 90% Confidence Interval at Hour 10 and 12 in Period 6 were relatively high. The following additional analyses may help understand what caused this result. In Period 6, at Hours 8, 10, 12, 14 and 24, the difference of Mean Change from Baseline calculated as Abemaciclib 600 mg minus Placebo was relatively large. This is because the mean change from baseline of four placebo subjects had a large decrease from baseline on average and that of seven Abemaciclib 600 mg subjects did not decrease, on average, as much or even slightly increased. Overall, the observed placebo effect was large in Period 6.

**Table 11: Observed  $\Delta$ QTcF,  $\Delta\Delta$ QTcF of Abemaciclib 400 mg and 600 mg (Cohort 2)**

|        |      | $\Delta$ QTcF: Mean of Change from Baseline<br>(Number of Subjects) |             | $\Delta\Delta$ QTcF : Difference of Mean<br>Change from Baseline |
|--------|------|---------------------------------------------------------------------|-------------|------------------------------------------------------------------|
| Period | Time | Abemaciclib 400 mg                                                  | Placebo     | Abemaciclib 600 mg – Placebo                                     |
| 5      | 2    | -5.5 (n=7)                                                          | -2.8 (n=7)  | -2.7                                                             |
| 5      | 4    | -1.8 (n=7)                                                          | -3.5 (n=7)  | 1.7                                                              |
| 5      | 6    | -9.1 (n=7)                                                          | -4.6 (n=6)  | -4.5                                                             |
| 5      | 8    | -14.7 (n=7)                                                         | -8.2 (n=6)  | -6.5                                                             |
| 5      | 10   | -10.2 (n=7)                                                         | -6.2 (n=6)  | -4.0                                                             |
| 5      | 12   | -11.5 (n=7)                                                         | -4.0 (n=7)  | -7.5                                                             |
| 5      | 14   | -9.6 (n=7)                                                          | -0.7 (n=6)  | -8.9                                                             |
| 5      | 24   | -18.6 (n=7)                                                         | -7.2 (n=6)  | -11.4                                                            |
| 6      | 2    | -12.9 (n=7)                                                         | -0.6 (n=4)  | -12.3                                                            |
| 6      | 4    | -9.0 (n=7)                                                          | -5.1 (n=4)  | -3.9                                                             |
| 6      | 6    | -13.3 (n=7)                                                         | -8.8 (n=4)  | -4.5                                                             |
| 6      | 8    | -11.8 (n=7)                                                         | -16.7 (n=4) | 4.9                                                              |
| 6      | 10   | -8.2 (n=7)                                                          | -17.3 (n=4) | 9.1                                                              |
| 6      | 12   | -6.2 (n=7)                                                          | -14.6 (n=4) | 8.4                                                              |
| 6      | 14   | -4.4 (n=7)                                                          | -10.6 (n=4) | 6.2                                                              |
| 6      | 24   | -17.1 (n=7)                                                         | -20.6 (n=4) | 3.5                                                              |
| Period | Time | Abemaciclib 600 mg                                                  | Placebo     | Abemaciclib 600 mg – Placebo                                     |
| 6      | 2    | -0.7 (n=4)                                                          | -0.6 (n=4)  | -0.1                                                             |
| 6      | 4    | -8.9 (n=4)                                                          | -5.1 (n=4)  | -3.8                                                             |
| 6      | 6    | -9.8 (n=4)                                                          | -8.8 (n=4)  | -1.0                                                             |
| 6      | 8    | -7.1 (n=4)                                                          | -16.7 (n=4) | 9.6                                                              |
| 6      | 10   | 4.7 (n=4)                                                           | -17.3 (n=4) | 22.0                                                             |
| 6      | 12   | 2.3 (n=4)                                                           | -14.6 (n=4) | 16.9                                                             |
| 6      | 14   | 0.8 (n=4)                                                           | -10.6 (n=4) | 11.4                                                             |
| 6      | 24   | -9.0 (n=4)                                                          | -20.6 (n=4) | 11.6                                                             |
| 7      | 2    | -7.4 (n=11)                                                         | -1.8 (n=4)  | -5.6                                                             |
| 7      | 4    | -8.8 (n=11)                                                         | -1.8 (n=4)  | -7.0                                                             |
| 7      | 6    | -12.0 (n=11)                                                        | -3.0 (n=4)  | -9.0                                                             |
| 7      | 8    | -11.9 (n=11)                                                        | -10 (n=4)   | -1.9                                                             |
| 7      | 10   | -10.2 (n=11)                                                        | -7.8 (n=4)  | -2.4                                                             |
| 7      | 12   | -6.7 (n=11)                                                         | -7.9 (n=4)  | 1.2                                                              |

|        |      | $\Delta$ QTcF: Mean of Change from Baseline<br>(Number of Subjects) |             | $\Delta\Delta$ QTcF : Difference of Mean<br>Change from Baseline |
|--------|------|---------------------------------------------------------------------|-------------|------------------------------------------------------------------|
| Period | Time | Abemaciclib 400 mg                                                  | Placebo     | Abemaciclib 600 mg – Placebo                                     |
| 7      | 14   | -7.9 (n=11)                                                         | -7.5 (n=5)  | -0.4                                                             |
| 7      | 24   | -17.3 (n=11)                                                        | -13.8 (n=3) | -3.5                                                             |

## 5.2.2 HR Analysis

HR was analyzed based on the same statistical model as in the primary analysis used for QTcF. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13. In Cohort 1, the largest upper limits of 90% CI for the HR mean differences between Abemaciclib 200 mg and placebo, Abemaciclib 300 mg and placebo, and Abemaciclib 400 mg and placebo were 5.9 bpm, 4.1 bpm and 6.0 bpm, respectively. In Cohort 2, the largest upper limits of 90% CI for the HR mean differences between Abemaciclib 200 mg and placebo and Abemaciclib 400 mg and placebo were 5.3 bpm and 9.2 bpm, respectively.

**Table 12: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Abemaciclib 200 mg, 300 mg and 400 mg (Cohort 1)**

| Cohort 1              | Time | $\Delta$ HR: Abemaciclib 400 mg |                                               | $\Delta$ HR: Placebo |                                               | $\Delta\Delta$ HR                                                           |
|-----------------------|------|---------------------------------|-----------------------------------------------|----------------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|                       |      | N                               | LS mean estimate<br>(90% Confidence Interval) | N                    | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of<br>Difference from Placebo<br>(90% Confidence Interval) |
| Abemaciclib<br>200 mg | 2    | 19                              | 0.6 (-1.6, 2.9)                               | 19                   | -2.4 (-4.2, -0.5)                             | 3.0 (0.1, 5.9)                                                              |
|                       | 4    | 20                              | 0.8 (-1.4, 3.0)                               | 19                   | 0.7 (-1.2, 2.6)                               | 0.1 (-2.8, 2.9)                                                             |
|                       | 6    | 19                              | 8.1 (5.9, 10.3)                               | 18                   | 7.7 (5.8, 9.6)                                | 0.4 (-2.5, 3.4)                                                             |
|                       | 8    | 19                              | 8.4 (6.2, 10.7)                               | 19                   | 9.2 (7.3, 11.1)                               | -0.8 (-3.7, 2.1)                                                            |
|                       | 10   | 19                              | 4.5 (2.3, 6.8)                                | 19                   | 5.9 (4.0, 7.8)                                | -1.4 (-4.3, 1.5)                                                            |
|                       | 12   | 19                              | 7.3 (5.1, 9.6)                                | 19                   | 11.4 (9.6, 13.3)                              | -4.1 (-7.0, -1.2)                                                           |
|                       | 14   | 20                              | 6.9 (4.7, 9.2)                                | 20                   | 8.4 (6.6, 10.3)                               | -1.5 (-4.4, 1.3)                                                            |
|                       | 24   | 19                              | 1.4 (-0.8, 3.7)                               | 19                   | 3.6 (1.8, 5.5)                                | -2.2 (-5.1, 0.7)                                                            |
| Abemaciclib<br>300 mg | 2    | 20                              | -1.0 (-3.0, 1.0)                              | 19                   | -2.4 (-4.2, -0.5)                             | 1.4 (-1.3, 4.1)                                                             |
|                       | 4    | 19                              | 0.8 (-1.2, 2.8)                               | 19                   | 0.7 (-1.2, 2.6)                               | 0.1 (-2.7, 2.8)                                                             |
|                       | 6    | 19                              | 6.5 (4.5, 8.5)                                | 18                   | 7.7 (5.8, 9.6)                                | -1.2 (-3.9, 1.6)                                                            |
|                       | 8    | 20                              | 8.3 (6.3, 10.3)                               | 19                   | 9.2 (7.3, 11.1)                               | -0.9 (-3.6, 1.8)                                                            |
|                       | 10   | 20                              | 4.6 (2.6, 6.6)                                | 19                   | 5.9 (4.0, 7.8)                                | -1.3 (-4, 1.4.0)                                                            |
|                       | 12   | 20                              | 9.3 (7.3, 11.3)                               | 19                   | 11.4 (9.6, 13.3)                              | -2.1 (-4.8, 0.6)                                                            |
|                       | 14   | 21                              | 5.2 (3.3, 7.2)                                | 20                   | 8.4 (6.6, 10.3)                               | -3.2 (-5.9, -0.6)                                                           |
|                       | 24   | 19                              | 1.5 (-0.5, 3.5)                               | 19                   | 3.6 (1.8, 5.5)                                | -2.2 (-4.9, 0.6)                                                            |
| Abemaciclib           | 2    | 20                              | 0.7 (-1.5, 2.9)                               | 19                   | -2.4 (-4.2, -0.5)                             | 3.1 (0.2, 6.0)                                                              |

| Cohort 1 | Time | ΔHR: Abemaciclib 400 mg |                                               | ΔHR: Placebo |                                               | ΔΔHR                                                                        |
|----------|------|-------------------------|-----------------------------------------------|--------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|          |      | N                       | LS mean estimate<br>(90% Confidence Interval) | N            | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of<br>Difference from Placebo<br>(90% Confidence Interval) |
| 400 mg   | 4    | 20                      | 1.2 (-1.0, 3.4)                               | 19           | 0.7 (-1.2, 2.6)                               | 0.5 (-2.4, 3.4)                                                             |
|          | 6    | 20                      | 7.1 (4.9, 9.3)                                | 18           | 7.7 (5.8, 9.6)                                | -0.6 (-3.5, 2.4)                                                            |
|          | 8    | 19                      | 7.2 (5.0, 9.5)                                | 19           | 9.2 (7.3, 11.1)                               | -2.0 (-4.9, 1.0)                                                            |
|          | 10   | 19                      | 5.4 (3.2, 7.6)                                | 19           | 5.9 (4.0, 7.8)                                | -0.5 (-3.5, 2.4)                                                            |
|          | 12   | 19                      | 9.0 (6.7, 11.2)                               | 19           | 11.4 (9.6, 13.3)                              | -2.5 (-5.4, 0.5)                                                            |
|          | 14   | 20                      | 5.5 (3.3, 7.7)                                | 20           | 8.4 (6.6, 10.3)                               | -2.9 (-5.8, 0.0)                                                            |
|          | 24   | 20                      | 2.2 (0.0, 4.4)                                | 19           | 3.6 (1.8, 5.5)                                | -1.4 (-4.3, 1.5)                                                            |

**Table 13: Analysis Results of ΔHR and ΔΔHR for Abemaciclib 400 mg and 600 mg (Cohort 2)**

| Cohort 2              | Time | ΔHR: Abemaciclib 400 mg |                                               | ΔHR: Placebo |                                               | ΔΔHR                                                                        |
|-----------------------|------|-------------------------|-----------------------------------------------|--------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|                       |      | N                       | LS mean estimate<br>(90% Confidence Interval) | N            | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of<br>Difference from Placebo<br>(90% Confidence Interval) |
| Abemaciclib<br>400 mg | 2    | 14                      | 0.5 (-2.5, 3.4)                               | 15           | 1.7 (-1.0, 4.4)                               | -1.2 (-5.1, 2.7)                                                            |
|                       | 4    | 14                      | 2.0 (-1, 4.9)                                 | 15           | 1.1 (-1.6, 3.8)                               | 0.9 (-3.0, 4.8)                                                             |
|                       | 6    | 14                      | 10.8 (7.9, 13.8)                              | 14           | 11.1 (8.3, 13.8)                              | -0.2 (-4.2, 3.7)                                                            |
|                       | 8    | 14                      | 6.0 (3.1, 9.0)                                | 14           | 8.8 (6.0, 11.5)                               | -2.7 (-6.7, 1.2)                                                            |
|                       | 10   | 14                      | 13.3 (10.4, 16.3)                             | 14           | 12.0 (9.2, 14.7)                              | 1.4 (-2.6, 5.3)                                                             |
|                       | 12   | 14                      | 7.5 (4.6, 10.4)                               | 15           | 11.0 (8.3, 13.7)                              | -3.5 (-7.4, 0.4)                                                            |
|                       | 14   | 14                      | 3.8 (0.9, 6.7)                                | 15           | 7.0 (4.3, 9.7)                                | -3.2 (-7.1, 0.7)                                                            |
|                       | 24   | 14                      | 11.7 (8.8, 14.7)                              | 13           | 12.5 (9.7, 15.4)                              | -0.8 (-4.8, 3.2)                                                            |
| Abemaciclib<br>600 mg | 2    | 15                      | 5.0 (2.0, 7.9)                                | 15           | 1.7 (-1.0, 4.4)                               | 3.3 (-0.8, 7.3)                                                             |
|                       | 4    | 15                      | 6.2 (3.3, 9.2)                                | 15           | 1.1 (-1.6, 3.8)                               | 5.1 (1.1, 9.2)                                                              |
|                       | 6    | 15                      | 12.5 (9.5, 15.4)                              | 14           | 11.1 (8.3, 13.8)                              | 1.4 (-2.7, 5.5)                                                             |
|                       | 8    | 15                      | 8.6 (5.6, 11.5)                               | 14           | 8.8 (6.0, 11.5)                               | -0.2 (-4.3, 3.9)                                                            |
|                       | 10   | 15                      | 13.3 (10.4, 16.3)                             | 14           | 12.0 (9.2, 14.7)                              | 1.4 (-2.7, 5.5)                                                             |
|                       | 12   | 15                      | 10.1 (7.1, 13.1)                              | 15           | 11.0 (8.3, 13.7)                              | -0.9 (-4.9, 3.2)                                                            |
|                       | 14   | 15                      | 9.8 (6.8, 12.7)                               | 15           | 7.0 (4.3, 9.7)                                | 2.8 (-1.3, 6.8)                                                             |
|                       | 24   | 15                      | 16.4 (13.5, 19.4)                             | 13           | 12.5 (9.7, 15.4)                              | 3.9 (-0.3, 8.0)                                                             |

### 5.2.3 PR Analysis

PR was analyzed based on the same statistical model as in the primary analysis used for QTcF. The point estimates and the 90% confidence intervals are presented in Table 14 and Table 15. In Cohort 1, the largest upper limits of 90% CI for the PR mean differences between Abemaciclib 200 mg and placebo, Abemaciclib 300 mg and placebo, and Abemaciclib 400 mg and placebo were 3.7 ms, 6.8 ms and 5.3 ms, respectively. In Cohort 2, the largest upper limits of 90% CI for the PR mean differences between Abemaciclib 200 mg and placebo and Abemaciclib 400 mg and placebo were 6.8 ms and 7.1 ms, respectively.

There was one subject (Subject ID 02007) who experienced PR greater than 200 ms at Hour 2, 4, 8, 10, 12 and 14 with the largest value of 206.0 ms in Period 6 when the subject was given Abemaciclib 600 mg.

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Abemaciclib 200 mg, 300 mg and 400 mg (Cohort 1)**

| Cohort 1           | Time | $\Delta$ PR: Abemaciclib 400 mg |                                            | $\Delta$ PR: Placebo |                                            | $\Delta\Delta$ PR                                                     |
|--------------------|------|---------------------------------|--------------------------------------------|----------------------|--------------------------------------------|-----------------------------------------------------------------------|
|                    |      | N                               | LS mean estimate (90% Confidence Interval) | N                    | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| Abemaciclib 200 mg | 2    | 19                              | -4.1 (-7.3, -0.9)                          | 19                   | -3.8 (-6.4, -1.2)                          | -0.3 (-4.4, 3.7)                                                      |
|                    | 4    | 20                              | -5.1 (-8.2, -2.0)                          | 19                   | -3.4 (-6.0, -0.8)                          | -1.7 (-5.7, 2.4)                                                      |
|                    | 6    | 19                              | -5.7 (-8.9, -2.5)                          | 18                   | -4.6 (-7.3, -2.0)                          | -1.0 (-5.1, 3.1)                                                      |
|                    | 8    | 19                              | -12.0 (-15.2, -8.8)                        | 19                   | -6.8 (-9.4, -4.2)                          | -5.2 (-9.3, -1.1)                                                     |
|                    | 10   | 19                              | -9.8 (-13.0, -6.6)                         | 19                   | -5.9 (-8.5, -3.3)                          | -3.9 (-8.0, 0.1)                                                      |
|                    | 12   | 19                              | -11.4 (-14.6, -8.2)                        | 19                   | -6.9 (-9.5, -4.3)                          | -4.6 (-8.6, -0.5)                                                     |
|                    | 14   | 20                              | -8.3 (-11.4, -5.1)                         | 20                   | -2.5 (-5.1, 0.0)                           | -5.7 (-9.8, -1.7)                                                     |
|                    | 24   | 19                              | -5.6 (-8.7, -2.4)                          | 19                   | -1.8 (-4.4, 0.8)                           | -3.7 (-7.8, 0.3)                                                      |
| Abemaciclib 300 mg | 2    | 20                              | -1.4 (-4.2, 1.4)                           | 19                   | -3.8 (-6.4, -1.2)                          | 2.4 (-1.4, 6.1)                                                       |
|                    | 4    | 19                              | -3.7 (-6.6, -0.9)                          | 19                   | -3.4 (-6.0, -0.8)                          | -0.3 (-4.1, 3.5)                                                      |
|                    | 6    | 19                              | -5.1 (-7.9, -2.3)                          | 18                   | -4.6 (-7.3, -2.0)                          | -0.4 (-4.3, 3.4)                                                      |
|                    | 8    | 20                              | -10.9 (-13.6, -8.1)                        | 19                   | -6.8 (-9.4, -4.2)                          | -4.1 (-7.9, -0.3)                                                     |
|                    | 10   | 20                              | -8.1 (-10.9, -5.3)                         | 19                   | -5.9 (-8.5, -3.3)                          | -2.2 (-6.0, 1.6)                                                      |
|                    | 12   | 20                              | -8.2 (-11, -5.4)                           | 19                   | -6.9 (-9.5, -4.3)                          | -1.3 (-5.1, 2.4)                                                      |
|                    | 14   | 21                              | -4.5 (-7.2, -1.7)                          | 20                   | -2.5 (-5.1, 0.0)                           | -1.9 (-5.6, 1.8)                                                      |
|                    | 24   | 19                              | 1.2 (-1.7, 4.0)                            | 19                   | -1.8 (-4.4, 0.8)                           | 3.0 (-0.8, 6.8)                                                       |
| Abemaciclib 400 mg | 2    | 20                              | -2.6 (-5.7, 0.6)                           | 19                   | -3.8 (-6.4, -1.2)                          | 1.2 (-2.9, 5.3)                                                       |
|                    | 4    | 20                              | -3.6 (-6.8, -0.5)                          | 19                   | -3.4 (-6.0, -0.8)                          | -0.2 (-4.3, 3.9)                                                      |
|                    | 6    | 20                              | -4.3 (-7.4, -1.1)                          | 18                   | -4.6 (-7.3, -2.0)                          | 0.4 (-3.8, 4.5)                                                       |
|                    | 8    | 19                              | -6.9 (-10.0, -3.7)                         | 19                   | -6.8 (-9.4, -4.2)                          | -0.1 (-4.2, 4.1)                                                      |

| Cohort 1 | Time | ΔPR: Abemaciclib 400 mg |                                               | ΔPR: Placebo |                                               | ΔΔPR                                                                        |
|----------|------|-------------------------|-----------------------------------------------|--------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|          |      | N                       | LS mean estimate<br>(90% Confidence Interval) | N            | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of<br>Difference from Placebo<br>(90% Confidence Interval) |
|          | 10   | 19                      | -7.7 (-10.8, -4.5)                            | 19           | -5.9 (-8.5, -3.3)                             | -1.8 (-5.9, 2.4)                                                            |
|          | 12   | 19                      | -6.1 (-9.2, -2.9)                             | 19           | -6.9 (-9.5, -4.3)                             | 0.8 (-3.3, 5.0)                                                             |
|          | 14   | 20                      | -4.6 (-7.7, -1.4)                             | 20           | -2.5 (-5.1, 0.0)                              | -2.0 (-6.1, 2.1)                                                            |
|          | 24   | 20                      | -1.9 (-5.1, 1.2)                              | 19           | -1.8 (-4.4, 0.8)                              | -0.1 (-4.2, 4.0)                                                            |

**Table 15: Analysis Results of ΔPR and ΔΔPR for Abemaciclib 400 mg and 600 mg (Cohort 2)**

| Cohort 2           | Time | ΔPR: Abemaciclib 400 mg |                                               | ΔPR: Placebo |                                               | ΔΔPR                                                                        |
|--------------------|------|-------------------------|-----------------------------------------------|--------------|-----------------------------------------------|-----------------------------------------------------------------------------|
|                    |      | N                       | LS mean estimate<br>(90% Confidence Interval) | N            | LS mean estimate<br>(90% Confidence Interval) | LS mean estimate of<br>Difference from Placebo<br>(90% Confidence Interval) |
| Abemaciclib 400 mg | 2    | 14                      | -1.1 (-5, 2.7)                                | 15           | -1.1 (-4.6, 2.4)                              | 0.0 (-5.1, 5.0)                                                             |
|                    | 4    | 14                      | -3.6 (-7.5, 0.2)                              | 15           | -1.1 (-4.6, 2.3)                              | -2.5 (-7.6, 2.5)                                                            |
|                    | 6    | 14                      | -4.3 (-8.1, -0.5)                             | 14           | -1.9 (-5.5, 1.6)                              | -2.4 (-7.5, 2.7)                                                            |
|                    | 8    | 14                      | -6.8 (-10.7, -3.0)                            | 14           | -5.3 (-8.9, -1.8)                             | -1.5 (-6.6, 3.6)                                                            |
|                    | 10   | 14                      | -3.0 (-6.8, 0.8)                              | 14           | -4.7 (-8.2, -1.1)                             | 1.7 (-3.4, 6.8)                                                             |
|                    | 12   | 14                      | -4.2 (-8.0, -0.4)                             | 15           | -4.4 (-7.9, -0.9)                             | 0.2 (-4.8, 5.2)                                                             |
|                    | 14   | 14                      | -3.4 (-7.2, 0.5)                              | 15           | -1.6 (-5.1, 1.9)                              | -1.8 (-6.8, 3.3)                                                            |
|                    | 24   | 14                      | -7.8 (-11.6, -4.0)                            | 13           | -5.8 (-9.5, -2.2)                             | -2.0 (-7.1, 3.2)                                                            |
| Abemaciclib 600 mg | 2    | 15                      | -3.5 (-7.4, 0.4)                              | 15           | -1.1 (-4.6, 2.4)                              | -2.4 (-7.8, 2.9)                                                            |
|                    | 4    | 15                      | -6.9 (-10.8, -3.0)                            | 15           | -1.1 (-4.6, 2.3)                              | -5.7 (-11.1, -0.4)                                                          |
|                    | 6    | 15                      | -6.2 (-10.1, -2.3)                            | 14           | -1.9 (-5.5, 1.6)                              | -4.3 (-9.7, 1.1)                                                            |
|                    | 8    | 15                      | -8.0 (-11.9, -4.1)                            | 14           | -5.3 (-8.9, -1.8)                             | -2.7 (-8, 2.7)                                                              |
|                    | 10   | 15                      | -5.7 (-9.6, -1.8)                             | 14           | -4.7 (-8.2, -1.1)                             | -1.0 (-6.4, 4.4)                                                            |
|                    | 12   | 15                      | -3.6 (-7.5, 0.3)                              | 15           | -4.4 (-7.9, -0.9)                             | 0.8 (-4.5, 6.1)                                                             |
|                    | 14   | 15                      | -3.1 (-7.0, 0.8)                              | 15           | -1.6 (-5.1, 1.9)                              | -1.5 (-6.8, 3.8)                                                            |
|                    | 24   | 15                      | -4.1 (-8.0, -0.2)                             | 13           | -5.8 (-9.5, -2.2)                             | 1.7 (-3.7, 7.1)                                                             |

#### 5.2.4 QRS Analysis

QRS was analyzed based on the same statistical model as in the primary analysis used for QTcF. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. In Cohort 1, the largest upper limits of 90% CI for the QRS mean differences between Abemaciclib 200 mg and placebo, Abemaciclib 300 mg and placebo,

and Abemaciclib 400 mg and placebo were 2.8 ms, 2.2 ms and 2.8 ms, respectively. In Cohort 2, the largest upper limits of 90% CI for the QRS mean differences between Abemaciclib 200 mg and placebo and Abemaciclib 400 mg and placebo were 2.6 ms and 4.2 ms, respectively.

No subject experienced >110 ms in QRS in either cohort.

**Table 16: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Abemaciclib 200 mg, 300 mg and 400 mg (Cohort 1)**

| Cohort 1           | Time | $\Delta$ QRS: Abemaciclib 400 mg |                                            | $\Delta$ QRS: Placebo |                                            | $\Delta\Delta$ QRS                                                    |
|--------------------|------|----------------------------------|--------------------------------------------|-----------------------|--------------------------------------------|-----------------------------------------------------------------------|
|                    |      | N                                | LS mean estimate (90% Confidence Interval) | N                     | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| Abemaciclib 200 mg | 2    | 19                               | 0.1 (-1.2, 1.5)                            | 19                    | 0.0 (-1.1, 1.1)                            | 0.1 (-1.6, 1.8)                                                       |
|                    | 4    | 20                               | -0.2 (-1.5, 1.1)                           | 19                    | -0.4 (-1.5, 0.7)                           | 0.2 (-1.5, 1.9)                                                       |
|                    | 6    | 19                               | 1.3 (0.0, 2.6)                             | 18                    | 1.6 (0.5, 2.7)                             | -0.3 (-2.0, 1.5)                                                      |
|                    | 8    | 19                               | -1.5 (-2.8, -0.2)                          | 19                    | -1 (-2.1, 0.1)                             | -0.5 (-2.2, 1.2)                                                      |
|                    | 10   | 19                               | -1.2 (-2.5, 0.2)                           | 19                    | -1.5 (-2.6, -0.4)                          | 0.4 (-1.3, 2.1)                                                       |
|                    | 12   | 19                               | -1.3 (-2.6, 0.1)                           | 19                    | -2.3 (-3.4, -1.2)                          | 1.0 (-0.7, 2.7)                                                       |
|                    | 14   | 20                               | -1.5 (-2.8, -0.2)                          | 20                    | -2.6 (-3.7, -1.5)                          | 1.1 (-0.6, 2.8)                                                       |
|                    | 24   | 19                               | -0.6 (-1.9, 0.7)                           | 19                    | -0.8 (-1.9, 0.3)                           | 0.2 (-1.5, 2.0)                                                       |
| Abemaciclib 300 mg | 2    | 20                               | 0.2 (-1.0, 1.4)                            | 19                    | 0.0 (-1.1, 1.1)                            | 0.2 (-1.4, 1.8)                                                       |
|                    | 4    | 19                               | -0.7 (-1.9, 0.5)                           | 19                    | -0.4 (-1.5, 0.7)                           | -0.2 (-1.9, 1.4)                                                      |
|                    | 6    | 19                               | 0.3 (-0.9, 1.5)                            | 18                    | 1.6 (0.5, 2.7)                             | -1.3 (-2.9, 0.3)                                                      |
|                    | 8    | 20                               | -1.3 (-2.5, -0.1)                          | 19                    | -1.0 (-2.1, 0.1)                           | -0.2 (-1.9, 1.4)                                                      |
|                    | 10   | 20                               | -2.8 (-4, -1.6)                            | 19                    | -1.5 (-2.6, -0.4)                          | -1.3 (-2.9, 0.3)                                                      |
|                    | 12   | 20                               | -3.4 (-4.5, -2.2)                          | 19                    | -2.3 (-3.4, -1.2)                          | -1.1 (-2.7, 0.5)                                                      |
|                    | 14   | 21                               | -2.6 (-3.7, -1.4)                          | 20                    | -2.6 (-3.7, -1.5)                          | 0.0 (-1.6, 1.6)                                                       |
|                    | 24   | 19                               | -0.3 (-1.5, 0.9)                           | 19                    | -0.8 (-1.9, 0.3)                           | 0.6 (-1.1, 2.2)                                                       |
| Abemaciclib 400 mg | 2    | 20                               | -0.2 (-1.5, 1.1)                           | 19                    | 0.0 (-1.1, 1.1)                            | -0.2 (-2.0, 1.5)                                                      |
|                    | 4    | 20                               | -1.6 (-2.9, -0.3)                          | 19                    | -0.4 (-1.5, 0.7)                           | -1.2 (-2.9, 0.6)                                                      |
|                    | 6    | 20                               | 0.1 (-1.2, 1.5)                            | 18                    | 1.6 (0.5, 2.7)                             | -1.4 (-3.2, 0.3)                                                      |
|                    | 8    | 19                               | -0.7 (-2.0, 0.6)                           | 19                    | -1.0 (-2.1, 0.1)                           | 0.3 (-1.4, 2.1)                                                       |
|                    | 10   | 19                               | -2.5 (-3.8, -1.2)                          | 19                    | -1.5 (-2.6, -0.4)                          | -0.9 (-2.7, 0.8)                                                      |
|                    | 12   | 19                               | -2.5 (-3.8, -1.2)                          | 19                    | -2.3 (-3.4, -1.2)                          | -0.2 (-2.0, 1.5)                                                      |
|                    | 14   | 20                               | -1.5 (-2.8, -0.2)                          | 20                    | -2.6 (-3.7, -1.5)                          | 1.1 (-0.7, 2.8)                                                       |
|                    | 24   | 20                               | -1.3 (-2.7, 0.0)                           | 19                    | -0.8 (-1.9, 0.3)                           | -0.5 (-2.2, 1.2)                                                      |

**Table 17: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Abemaciclib 400 mg and 600 mg (Cohort 2)**

| Cohort 2           | Time | $\Delta$ QRS: Abemaciclib 400 mg |                                            | $\Delta$ QRS: Placebo |                                            | $\Delta\Delta$ QRS                                                    |
|--------------------|------|----------------------------------|--------------------------------------------|-----------------------|--------------------------------------------|-----------------------------------------------------------------------|
|                    |      | N                                | LS mean estimate (90% Confidence Interval) | N                     | LS mean estimate (90% Confidence Interval) | LS mean estimate of Difference from Placebo (90% Confidence Interval) |
| Abemaciclib 400 mg | 2    | 14                               | -1.4 (-3.1, 0.3)                           | 15                    | -0.4 (-2.0, 1.1)                           | -1.0 (-3.2, 1.2)                                                      |
|                    | 4    | 14                               | -0.8 (-2.5, 0.9)                           | 15                    | -1.0 (-2.5, 0.5)                           | 0.2 (-2.0, 2.4)                                                       |
|                    | 6    | 14                               | -1.8 (-3.5, -0.1)                          | 14                    | -1.1 (-2.6, 0.5)                           | -0.7 (-3.0, 1.5)                                                      |
|                    | 8    | 14                               | -2.0 (-3.7, -0.3)                          | 14                    | -2.3 (-3.9, -0.8)                          | 0.4 (-1.9, 2.6)                                                       |
|                    | 10   | 14                               | -2.0 (-3.7, -0.3)                          | 14                    | -2.1 (-3.7, -0.6)                          | 0.1 (-2.1, 2.3)                                                       |
|                    | 12   | 14                               | -2.4 (-4.1, -0.7)                          | 15                    | -2.1 (-3.7, -0.6)                          | -0.3 (-2.5, 2.0)                                                      |
|                    | 14   | 14                               | -1.8 (-3.5, -0.1)                          | 15                    | -1.5 (-3.0, 0.1)                           | -0.4 (-2.6, 1.8)                                                      |
|                    | 24   | 14                               | -3.2 (-4.9, -1.5)                          | 13                    | -2.2 (-3.8, -0.6)                          | -1.0 (-3.2, 1.3)                                                      |
| Abemaciclib 600 mg | 2    | 15                               | -1.3 (-3.0, 0.4)                           | 15                    | -0.4 (-2.0, 1.1)                           | -0.9 (-3.2, 1.5)                                                      |
|                    | 4    | 15                               | -1.5 (-3.2, 0.3)                           | 15                    | -1.0 (-2.5, 0.5)                           | -0.5 (-2.8, 1.9)                                                      |
|                    | 6    | 15                               | -1.5 (-3.2, 0.2)                           | 14                    | -1.1 (-2.6, 0.5)                           | -0.5 (-2.8, 1.9)                                                      |
|                    | 8    | 15                               | -2.5 (-4.3, -0.8)                          | 14                    | -2.3 (-3.9, -0.8)                          | -0.2 (-2.6, 2.2)                                                      |
|                    | 10   | 15                               | -0.4 (-2.2, 1.3)                           | 14                    | -2.1 (-3.7, -0.6)                          | 1.7 (-0.7, 4.1)                                                       |
|                    | 12   | 15                               | -0.3 (-2.0, 1.5)                           | 15                    | -2.1 (-3.7, -0.6)                          | 1.9 (-0.5, 4.2)                                                       |
|                    | 14   | 15                               | -0.8 (-2.5, 1.0)                           | 15                    | -1.5 (-3.0, 0.1)                           | 0.7 (-1.7, 3.1)                                                       |
|                    | 24   | 15                               | -1.8 (-3.5, -0.1)                          | 13                    | -2.2 (-3.8, -0.6)                          | 0.4 (-2.0, 2.8)                                                       |

### 5.2.5 Categorical Analysis

This reviewer confirmed the analysis results provided in the Sponsor's report, which is shown in Table 1. In Cohort 1, there were no subjects who experienced >450 ms in QTcF, >30 ms in  $\Delta$ QTcF, >200 ms in PR or >110 ms in QRS. In Cohort 2, as consistent with the results shown in the Sponsor's table, two subjects administered Abemaciclib 400 mg (Subject ID: 02002 and 02004) had more than 400 ms one time point, another subject (Subject ID: 02001) administered Abemaciclib 600 mg experienced >450 ms in QTcF and >30 ms in  $\Delta$ QTcF at one time point, and another subject (Subject ID: 02007) administered Abemaciclib 600 mg experienced >200 ms in PR at six time points (Hours 2, 4, 8, 10, 12 and 14) of Period 7.

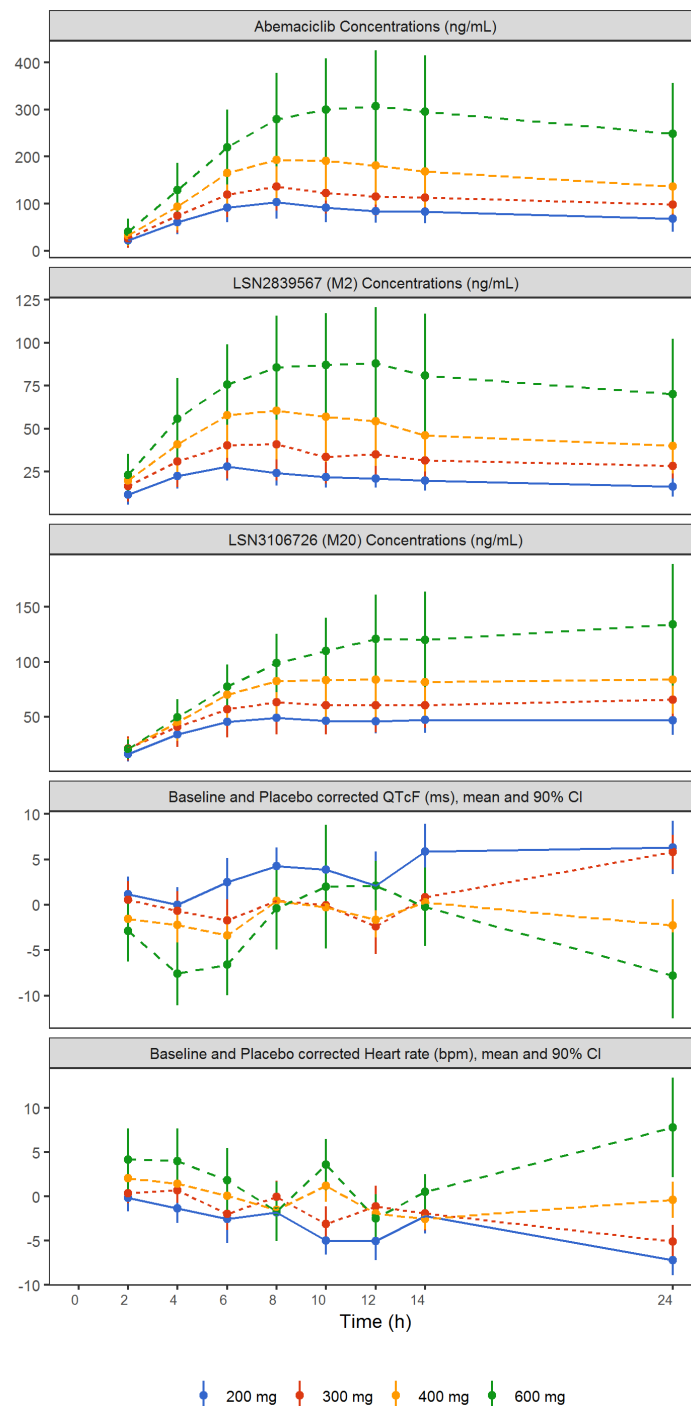
## 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

In all the following analyses ECG/PK data from period 4 of cohort 2 (loperamide DDI assessment) have been excluded.

Figure 7 shows the comparison of drug concentration, metabolites concentrations,  $\Delta\Delta$ QTcF and  $\Delta\Delta$ HR for each of the sampling time points. There were no significant

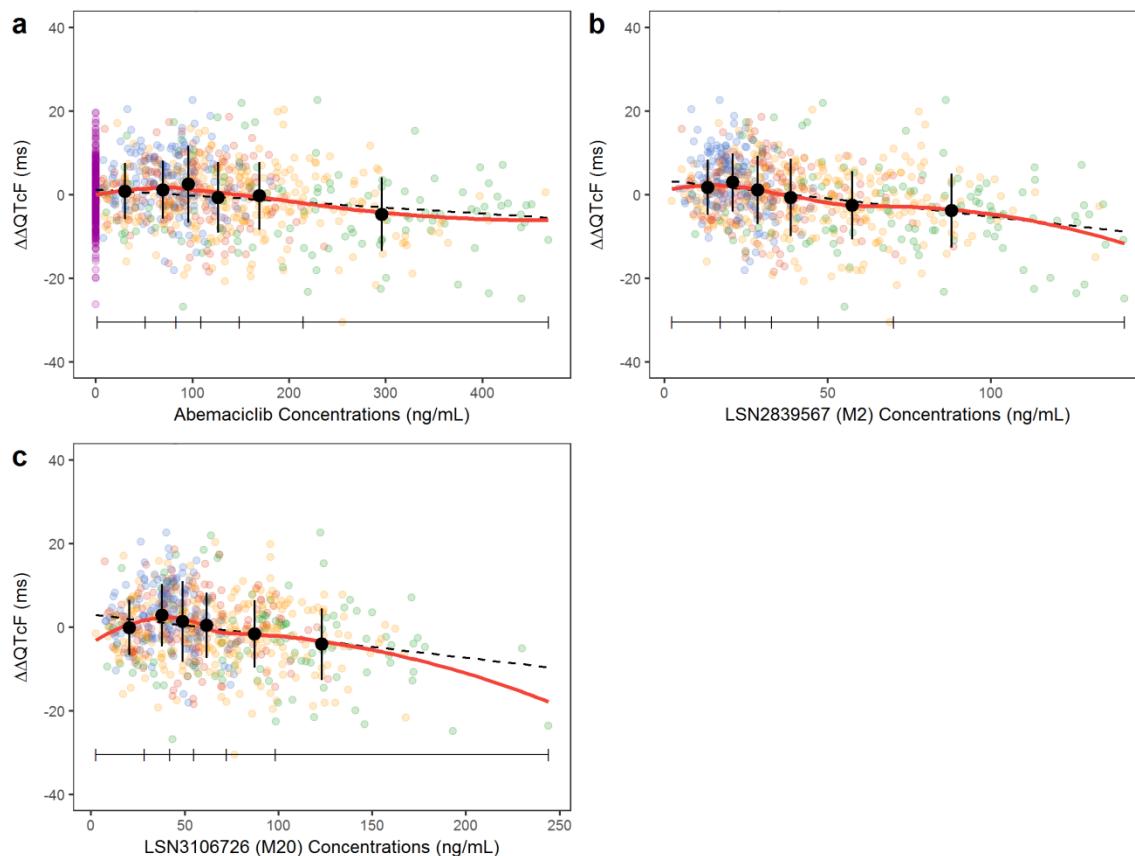
changes in heart rate (>10 bpm) and there was no systematic delay between PK and QTcF effects. However, there was a slight increase in mean  $\Delta\Delta\text{QTcF}$  effects seen at delayed time (24 h), but there was no dose-dependent relationship seen in this effect (effect with 5 mg dose higher than up to a 30-fold higher dose).

**Figure 7: Time-course of drug concentration, metabolites concentrations,  $\Delta\Delta\text{QTcF}$ , and  $\Delta\Delta\text{HR}$ . Error bars illustrate mean  $\pm$  SD for concentration and 90% CI for  $\Delta\Delta\text{QTcF}$  and  $\Delta\Delta\text{HR}$**



Graphical assessment of linearity of the C-QTc relationship using drug concentration versus  $\Delta\Delta QTcF$  plot did not show any systematic non-linearity in the data (Figure 8).

**Figure 8: Assessment of linearity of C-QTc using  $\Delta\Delta QTcF$  vs. Abemaciclib (A) and Metabolites M2(B) and M20 (C) concentration scatter plot, stratified by dose**



The concentration-QTc relationship was therefore evaluated using the prespecified model:

$$\Delta QTc = \text{TIME} + \text{CONC} + \text{ACTIVE} + QTc_{\text{baseline}} + (\text{CONC}|\text{USUBJID})$$

where time, study and active are three categorical variables representing nominal time post-dose, treatment arm (active=1 for drug, active=0 for placebo), QTc baseline centered at study average. Please note concentration values for placebo are set to zero. In this model conc|usubjid (last term) denotes that there is a random effect on both the intercept and the slope with an unstructured covariance.

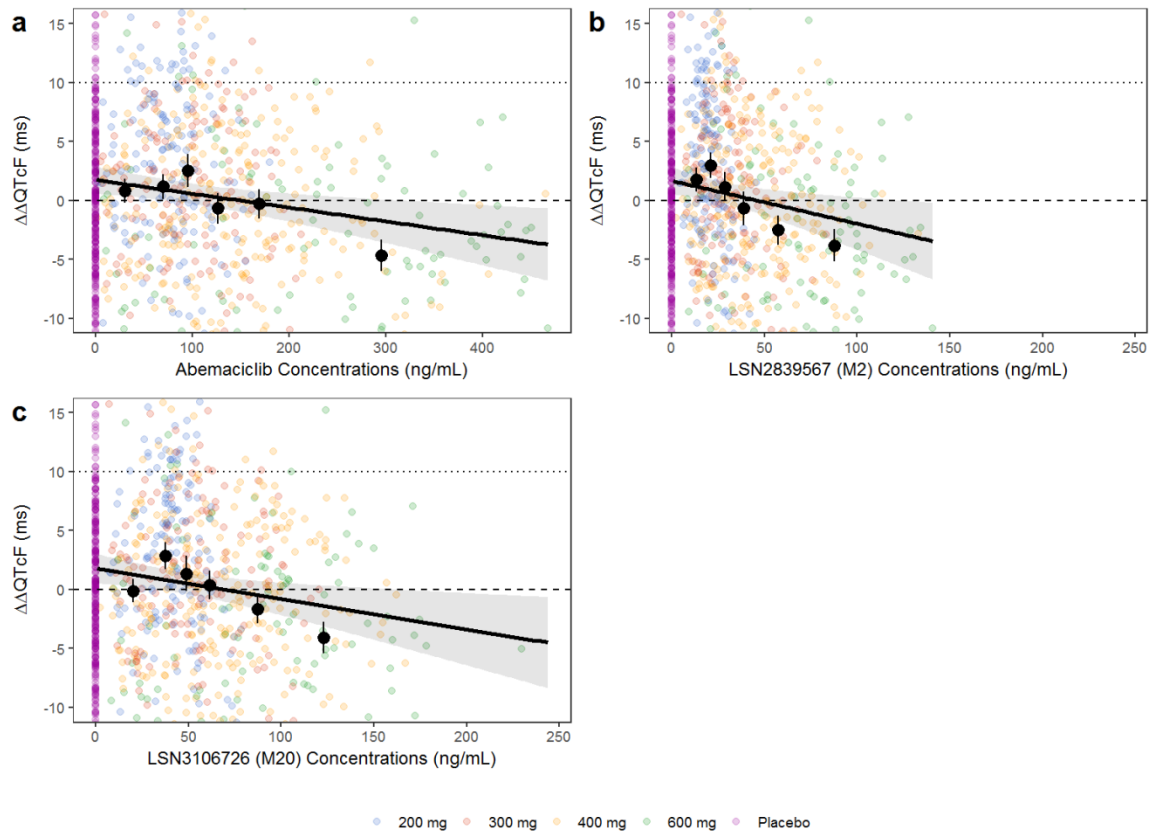
The goodness-of-fit plot for the model is shown in Figure 8, which shows that the model describes the observed data reasonably well and suggests an absence of a relationship between any of the major moieties and QTc. However, of note the  $C_{\text{max}}$  of the highest dose group (600 mg) is lower than the  $C_{\text{max,ss}}$  for M2 ( $C_{\text{max,600 mg}}$ : 96 ng/mL ;  $C_{\text{max,ss}}$ : 128 ng/mL<sup>1</sup>) and M20 ( $C_{\text{max,600 mg}}$ : 132 ng/mL;  $C_{\text{max,ss}}$ : 197 ng/mL<sup>2</sup>).

<sup>1</sup> [Summary of Clinical Pharmacology Appendix](#) Table APP.2.7.2.6

<sup>2</sup> [Summary of Clinical Pharmacology Appendix](#) Table APP.2.7.2.7

Further evaluation of model performance using model diagnostic plots (see Appendix 6.2) supports this observation. Lastly, estimated model parameters are included in Appendix 6.3.

**Figure 9: Goodness-of-fit plot for the model: (A) abemaciclib, (B) M2 and (C) M20.** The colors correspond to placebo and different treatment groups. The observed  $\Delta\Delta\text{QTcF}$  is grouped into 10 bins for the treatment data. The solid line and shaded area represents mean  $\pm$  90% confidence interval and the line in the bottom represents the concentration range in the bins, where the dot represents the median for each bin. Note, that  $\Delta\Delta\text{QTcF}$  is computed by subtracting the average placebo by-time from  $\Delta\text{QTcF}$ .



## 5.4 ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 5.4.2 ECG assessments

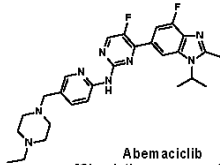
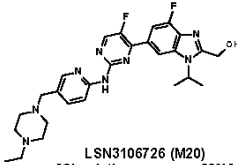
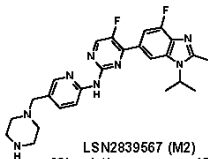
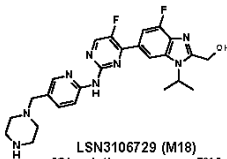
Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 Other ECG Intervals**

No clinically relevant effect on heart rate, PR or QRS intervals.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

| Pharmacology        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mechanism of Action | <p>Abemaciclib is an inhibitor of cyclin D-dependent kinases 4 and 6 (CDK4 and CDK6) and was most active against cyclin D1/CDK4 in enzymatic assays. In breast cancer, cyclin D1/CDK4 has been shown to promote phosphorylation of the retinoblastoma protein (Rb), cell proliferation, and tumor growth. Abemaciclib prevents Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth in preclinical models following short duration target inhibition. In estrogen receptor-positive breast cancer cell lines, sustained target inhibition by abemaciclib prevents rebound of Rb phosphorylation and cell cycle reentry, resulting in senescence and apoptosis. In vivo, abemaciclib monotherapy dosed daily without interruption at clinically relevant concentrations in breast cancer xenograft models resulted in reduction of tumor size.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Active Moieties     | <p>Abemaciclib and oxidative metabolites LSN28394567 (M2) and LSN3106726 (M20) constitute the majority (73%) of the drug-related exposure in human plasma, with oxidative metabolite LSN3106729 (M18) contributing to a lesser amount (5%). All 3 metabolites are active in enzyme binding biochemical assays with potency similar to abemaciclib.</p> <p>The figure below shows abemaciclib and active metabolites identified in plasma. Their mean circulating exposure (<math>AUC_{0-\infty}</math> as % total plasma radioactivity exposure) and excreted amount from feces (as % total dose administered) are following a single, oral 150-mg dose of abemaciclib in healthy subjects (Study I3Y-MC-JPBD [JPBD]).</p> <div><div><div><p>Abemaciclib<br/>[Circulating exposure 34%]<br/>[Dose excreted 6.76%]</p></div><div><p>LSN3106726 (M20)<br/>[Circulating exposure 26%]<br/>[Dose excreted 3.88%]</p></div></div><div><div><p>LSN28394567 (M2)<br/>[Circulating exposure 13%]<br/>[Dose excreted 32.30%]</p></div><div><p>LSN3106729 (M18)<br/>[Circulating exposure 5%]<br/>[Dose excreted 4.22%]</p></div></div></div> |

| Pharmacology        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| QT Prolongation     | <p>Study I3Y-MC-JPCA (JPCA) was a Phase 1, randomized, single-blind, placebo-controlled, single ascending dose crossover study in healthy subjects conducted to determine the relationship between plasma concentrations of abemaciclib, M2, and M20 and QT interval following single oral doses of abemaciclib.</p> <p>The relationship between plasma concentrations of abemaciclib and its major active metabolites and <math>\Delta\Delta QTcF</math> were evaluated using a linear mixed-effects model. The slopes of <math>\Delta\Delta QTcF</math> and abemaciclib, M2, M20, and total active species concentrations were not statistically different from 0 (p-value &gt;.05). In addition, the upper bound of the 90% CI of the predicted <math>\Delta\Delta QTcF</math> did not cross the 10-msec threshold at the highest observed concentrations of abemaciclib, total active species, M2, and M20. Therefore, abemaciclib does not prolong the QT interval to any clinically relevant extent.</p> <p>The nonclinical cardiovascular risk assessment consisted of in-vitro assessment of human ether-á-go-go-related gene (hERG) potassium channel potential blockage and a cardiovascular safety pharmacology study in dogs. The in-vitro hERG half-maximal inhibitory concentration (<math>IC_{50}</math>) was estimated to be greater than 1.65 <math>\mu M</math> (solubility of abemaciclib limited testing higher concentrations), compared to the human steady-state maximal concentration (<math>C_{max,ss}</math>) at 200-mg twice daily of 0.59 <math>\mu M</math>. In addition, Lilly conducted an assessment of the potential for metabolites M2 and M20 to interfere with the hERG channel. The <math>IC_{50}</math> for hERG inhibition of both metabolites was estimated to be greater than 10 <math>\mu M</math> (the highest concentration tested), which is approximately 25-fold higher than the human <math>C_{max}</math> for M20 (which has higher exposure in humans than M2) at 200-mg twice-daily abemaciclib.</p> <p>No QTc prolongation was observed in dogs at doses up to 10 mg/kg. Exposure (<math>C_{max}</math>) in dogs after a single 10-mg/kg dose is similar to the human <math>C_{max}</math> after a single 200-mg dose.</p> |
| General Information |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Bioanalysis         | <p>Plasma samples collected in clinical studies were analyzed for abemaciclib and its active metabolites LSN2839567 (M2) and LSN3106726 (M20) using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The LLOQ was 1 ng/mL and the upper limit of quantitation was 500 ng/mL for all analytes, with the exception of [<math>^{13}C_8</math>]-abemaciclib, for which the LLOQ was 0.002 ng/mL and the ULOQ was 2 ng/mL. Samples above the ULOQ were diluted and reanalyzed to yield results within the calibrated range. Both precision and accuracy, as expressed by relative standard deviation and relative error, met the criteria of <math>\leq 15\%</math> and <math>\pm 15.0\%</math> respectively, across the standard curve range for all analytes. Quality control samples across the standard curve range were included in each sample analysis batch. Incurred sample reanalysis (ISR) was conducted for several of the abemaciclib clinical studies and results indicated that the assay method performed according to established ISR acceptance criteria.</p> <p>The plasma method was modified for cerebrospinal fluid to measure concentrations of abemaciclib and active metabolites M2 and M20 in cerebrospinal fluid samples collected from a subset of patients with brain metastases.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| General Information                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Exposure in Healthy vs. Patients</b>                                       | Abemaciclib PK were similar in healthy subjects and cancer patients. The mean $AUC_{0-\infty}$ was 3890 ng·hr/mL (47.1% CV) and 4420 ng·hr/mL (58.6% CV) in healthy subjects and cancer patients, respectively. Mean $C_{max}$ was 113 ng/mL (48.4% CV) and 123 ng/mL (77.1% CV) in healthy subjects and cancer patients, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Drug Exposure at Steady State Following the Therapeutic Dosing Regimen</b> | <p>The PopPK model-estimated mean <math>C_{max,ss}</math>, <math>C_{min,ss}</math>, and <math>AUC_{\tau,ss}</math>, calculated based on the average dose received (190 mg) throughout the study, were 258 ng/mL (50% CV), 180 ng/mL (60% CV), and 2608 ng·hr/mL (61% CV), respectively, for 200-mg twice-daily dosing in patients in Study I3Y-MC-JPBN (MONARCH 1).</p> <p>The PopPK model-estimated mean <math>C_{max,ss}</math>, <math>C_{min,ss}</math>, and <math>AUC_{\tau,ss}</math>, calculated based on the average dose received (145 mg) throughout the study, were 179 ng/mL (38% CV), 97.2 ng/mL (62% CV), and 1600 ng·hr/mL (48% CV), respectively, for 150-mg twice-daily dosing in Study I3Y-MC-JPBL (MONARCH 2).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Range of Effective Dose or Exposure</b>                                    | <p>The abemaciclib dosage regimen of 200 mg twice daily as a single agent and 150 mg twice daily in combination with fulvestrant, with dose reductions for safety and tolerability in 50-mg units to a lowest possible dose of 50 mg twice daily is recommended for clinical use.</p> <p>In the single-agent setting of MONARCH 1, given the absence of a statistically significant relationship between exposure and objective response rate (ORR) or progression-free survival (PFS), the high inter-individual variability in PK that leads to extensive overlap in the range of exposures achieved by doses of 50 mg to 200 mg twice daily, and the number of patients experiencing a partial response who also required a dose reduction, the recommended dose reductions for individual tolerability are appropriate for patients who cannot tolerate higher doses.</p> <p>In the setting of combination with fulvestrant in MONARCH 2, there was a positive linear relationship between abemaciclib exposure and tumor shrinkage and also PFS. Higher abemaciclib concentrations were associated with larger reductions in tumor size and also with longer PFS. The average doses administered in the group of patients who started at doses of 200 mg twice daily and 150 mg twice daily were 176 mg and 146 mg, respectively. Taking dose reductions into account, the average dose administered was similar between the 2 starting doses. The efficacy observed, regardless of the starting dose, was also similar. The overall impact of dose reductions as implemented in MONARCH 2 after a 150-mg starting dose was a small decrease in survival time, estimated at 0.9 months (4.6%).</p> |
| <b>Maximally Tolerated Dose or Exposure</b>                                   | <p>In patients, the maximum tolerated dose is 200 mg twice daily, where mean <math>AUC_{\tau,ss}</math> is 3510 ng·hr/mL (38% CV) in MONARCH 1, and is 3580 ng·hr/mL (40% CV) in MONARCH 2.</p> <p>In healthy subjects, the maximum tolerated single dose is 400 mg, where mean <math>AUC_{0-\infty}</math> is 7840 ng·hr/mL (47% CV).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| General Information                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dose Proportionality</b>                                  | <p>In Study I3Y-MC-JPBA (JPBA), over the single dose range of 50 mg (0.25 ratio to the proposed (b) (4) starting dose) to 275 mg (1.375 ratio to the proposed (b) (4) starting dose) in cancer patients, the mean abemaciclib <math>C_{max}</math> and <math>AUC_{0-\infty}</math> values increased approximately proportional to dose. For a ratio of doses of 5.5 (ratio of 275 mg to 50 mg), the ratios for dose-normalized <math>C_{max}</math> and <math>AUC_{0-\infty}</math> were 1.11 (90% CI, 0.64-1.91) and 1.61 (90% CI, 0.85-3.05). Although the mean ratios were greater than 1, the 90% CIs included 1; therefore, mean increase in exposure with a single dose is concluded to be dose proportional.</p> <p>Also in Study JPBA, following multiple twice daily dosing over the range of 75 mg (0.375 ratio to the proposed (b) (4) starting dose) to 200 mg (proposed (b) (4) starting dose) in cancer patients, the mean abemaciclib <math>C_{max}</math> and <math>AUC_{0-\tau}</math> values increased approximately proportional to dose. The ratios for dose normalized <math>C_{max}</math> and <math>AUC_{0-\tau}</math> were 0.84 (90% CI, 0.38-1.83) and 0.96 (90% CI, 0.43-2.13). Although the mean ratios were slightly less than 1, the 90% CIs included 1; therefore, mean increase in exposure with multiple dosing is concluded to be dose proportional.</p> <p>In Study JPCA, linear and dose-proportional PK were observed over the single-dose range of 200 mg (the proposed (b) (4) starting dose) to 600 mg (3.0 ratio to the proposed (b) (4) starting dose) in healthy subjects.</p> |
| <b>Accumulation of exposure over repeated administration</b> | Steady state is reached after 5 days of twice daily dosing. The accumulation ratio after twice daily administration is approximately 3.3- and 4.6-fold, based on maximum observed drug concentration ( $C_{max}$ ) and area under the concentration versus time curve (AUC), respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Variability in exposure</b>                               | Exposures of abemaciclib among cancer patients are highly variable (77.1% CV for $C_{max}$ and 58.6% CV for AUC).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Absorption                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Bioavailability</b>                                       | The absolute bioavailability of a 200-mg oral dose of abemaciclib is 45% (90% CI, 40%-51%) (Study I3Y-MC-JPBS [JPBS]).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b><math>t_{max}</math></b>                                  | <p><b>Median (range) after a single 150-mg tablet administration of abemaciclib in healthy subjects (N=13):</b></p> <ul style="list-style-type: none"> <li>Abemaciclib <math>t_{max}</math> = 8.00 hours (6.00-12.00)</li> <li>LSN2839567 (M2) <math>t_{max}</math> = 6.00 hours (4.00-10.00)</li> <li>LSN3106726 (M20) <math>t_{max}</math> = 8.00 hours (6.00-24.00)</li> </ul> <p><b>Median (range) at steady state, after repeated twice daily (Q12H) 150 mg capsule administration of abemaciclib in cancer patients (N=72):</b></p> <ul style="list-style-type: none"> <li>Abemaciclib <math>t_{max,ss}</math> = 3.95 hours (0-10.15)</li> <li>LSN2839567 (M2) <math>t_{max,ss}</math> = 3.85 hours (0-10.15)</li> <li>LSN3106726 (M20) <math>t_{max,ss}</math> = 3.93 hours (0-10.00)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| Absorption                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                      |                                                                                                       |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Food Effect                     | AUC <sub>0-∞</sub> (ng·hr/mL)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | C <sub>max</sub> (ng/mL)                                                             | t <sub>max</sub> (hr) (range)                                                                         |
|                                 | Geometric Mean Ratio<br>(fed n=23, fast n=24)<br>(90% CI)<br><br>= 1.13 (1.05, 1.22)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Geometric Mean Ratio<br>(fed n=23, fast n=24)<br>(90% CI)<br><br>= 1.30 (1.20, 1.40) | Median Difference<br>(fed n=23, fast n=23)<br>(90% CI)<br><br>= 0 (-2.00, 0)<br><br>Medians = 8.00 hr |
|                                 | Following administration of a single 150-mg tablet of abemaciclib in healthy subjects, a high-fat meal increased the mean AUC <sub>0-∞</sub> and C <sub>max</sub> of abemaciclib by 13% and 30%, respectively; with no change in median t <sub>max</sub> (Study I3Y-MC-JPCC [JPCC]). Administration with meals is not associated with a clinically relevant effect on exposure. Abemaciclib may be administered without regard to meals.                                                                                                                                        |                                                                                      |                                                                                                       |
| Distribution                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                      |                                                                                                       |
| Volume of Distribution          | Geometric means after a single dose of abemaciclib in cancer patients based on noncompartmental analysis: <ul style="list-style-type: none"><li>150 mg dose (N=85): Abemaciclib V<sub>ss</sub>/F = 1310 L (73% CV)</li><li>200 mg dose (N=117): Abemaciclib V<sub>ss</sub>/F = 1300 L (96% CV)</li></ul>                                                                                                                                                                                                                                                                        |                                                                                      |                                                                                                       |
| Plasma Protein Binding          | Abemaciclib is highly bound (approximately 96% to 98%) to proteins in human plasma. Binding appeared to be independent of concentration from 0.3 μM (152 ng/mL) to 10 μM (5066 ng/mL). The major active metabolites M2 and M20 in general are less bound (approximately 89% to 94%) than abemaciclib. Abemaciclib binds to both serum albumin and alpha-1-acid glycoprotein.                                                                                                                                                                                                    |                                                                                      |                                                                                                       |
| As Substrate of Transporters    | In vitro, abemaciclib is a substrate of P-gp and BCRP. In vivo, abemaciclib is cleared primarily through metabolism. Therefore, inhibitors or inducers of P-gp or BCRP are unlikely to have clinically significant effect on the disposition of abemaciclib. In vitro, abemaciclib, M2, and M20 are not substrates for human hepatic transporters, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, and organic cation transporter 1 (OCT1).                                                                                                                      |                                                                                      |                                                                                                       |
| Elimination                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                      |                                                                                                       |
| Terminal Elimination Half-Life  | Geometric mean (%CV) half-life after a single 200-mg dose in cancer patients (N=421): <ul style="list-style-type: none"><li>Abemaciclib t<sub>1/2</sub> = 24.8 hours (52.1%)</li><li>M2 t<sub>1/2</sub> = 19.3 hours (65.4%)</li><li>M20 t<sub>1/2</sub> = 17.5 hours (62.5%)</li></ul> Geometric mean (%CV) half-life after a single 150-mg dose in cancer patients (N=326): <ul style="list-style-type: none"><li>Abemaciclib t<sub>1/2</sub> = 17.5 hours (46.0%)</li><li>M2 t<sub>1/2</sub> = 17.2 hours (65.1%)</li><li>M20 t<sub>1/2</sub> = 14.0 hours (62.5%)</li></ul> |                                                                                      |                                                                                                       |
| Effective Elimination Half-Life | For abemaciclib, the effective half-life and terminal half-life are the same.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                      |                                                                                                       |

| Metabolism                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Fraction Metabolized (% dose)</b>           | Of the 75% of the administered dose excreted in feces profiled, approximately 7% was identified as the unchanged parent compound and 52% as metabolites. The fraction of abemaciclib metabolized by CYP3A is estimated to be approximately 0.89.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Primary Metabolic Pathway(s)</b>            | The major biotransformation pathway for abemaciclib involves N-desethylation of the piperazine ring to form the active metabolite M2. Minor pathways include hydroxylation of abemaciclib to form other active metabolite M20 and subsequent N-desethylation leading to the formation of M18.<br><br>Abemaciclib is extensively metabolized primarily by CYP3A.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Excretion                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Primary Excretion Pathways (% dose) ±SD</b> | Abemaciclib is cleared primarily by hepatic elimination. Of the 84.4% of the administered dose recovered, approximately 81% of the dose was excreted in the feces and approximately 3.4% excreted in urine. The majority of the dose excreted in feces constituted metabolites.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Interaction liability (Drug as perpetrator)    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Inhibition/Induction of Metabolism</b>      | <p>Abemaciclib and its major (&gt;10% drug-related exposure) metabolites, M2 and M20, do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.</p> <p>Abemaciclib and its major metabolites M2 and M20 do not induce CYP1A2, CYP2B6, and CYP3A.</p> <p>Abemaciclib and its major metabolites, M2 and M20, cause down-regulation of mRNA of CYPs in cultured human hepatocytes:</p> <ul style="list-style-type: none"> <li>• Abemaciclib caused decreases in CYP1A2, CYP2B6, CYP2D6, CYP3A4, and CYP3A5 mRNA.</li> <li>• M2 caused similar decreases in CYP1A2, CYP2B6, CYP2C9, and CYP3A4 mRNA.</li> <li>• M20 caused similar decreases in CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A4, and CYP3A5 mRNA.</li> <li>• The mechanism and clinical relevance of mRNA down-regulation are not presently understood.</li> <li>• Autoinhibition of abemaciclib metabolism has not been observed in humans; therefore, a clinically relevant drug interaction with CYP3A substrates is unlikely.</li> </ul> |

| Interaction liability (Drug as perpetrator)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Inhibition/Induction of Transporter Systems</b> | <p>Abemaciclib is a substrate and P-gp and BCRP. Abemaciclib and its major metabolites M2 and M20 do not inhibit hepatic transporters OCT1, OATP1B1, and OATP1B3 at clinically relevant concentrations.</p> <p>Abemaciclib was shown to inhibit P-gp in humans as indicated by increased loperamide AUC and <math>C_{max}</math> in Study JPCA. Abemaciclib inhibits P-gp and BCRP in vitro. Study JPCA confirmed that abemaciclib inhibits P-gp in vivo using the P-gp substrate loperamide, which is a commonly used concomitant medication with abemaciclib. There was a small, but statistically significant, increase in loperamide exposure based on <math>AUC_{0-12h}</math> (13%), <math>AUC_{0-\infty}</math> (9%), and <math>C_{max}</math> (35%). The small increase observed in loperamide exposure was not considered to be a clinically meaningful PK effect of abemaciclib on loperamide, as the change was within the wide therapeutic margin (Vandenbossche et al. 2010). Given the above and the fact that loperamide did not alter the PK of abemaciclib and its active metabolites, abemaciclib can be safely coadministered with loperamide. Abemaciclib has not been studied with narrow therapeutic index substrates of P-gp; therefore, caution should be used when coadministering such drugs with abemaciclib.</p> <p>In vitro, abemaciclib and its major metabolites M2 and M20 do not inhibit renal transporters, OAT1 and OAT3, but do inhibit OCT2, MATE1 and MATE2-K at clinically relevant concentrations. In humans, abemaciclib significantly increased metformin exposure compared to placebo, with increases in <math>AUC_{0-\infty}</math> and <math>C_{max}</math> by 37% and 22%, respectively, and significantly decreased metformin CL, with decreases in <math>CL_R</math> and <math>CL_{RS}</math> of 45% (<math>CL_R</math> ratio 0.550) and 62% (<math>CL_{RS}</math> ratio 0.381), respectively (Study JPCK). The metformin <math>t_{max}</math> was increased by 0.5 hours. These findings are consistent with abemaciclib inhibition of the transporters OCT2, MATE1, and MATE2-K, which are involved in the active tubular secretion of both metformin and endogenous creatinine.</p> |
| Interaction liability (Drug as Victim)             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Effect of CYP3A Inhibitors</b>                  | <p>In Study I3Y-MC-JPBE (JPBE), coadministration of multiple 500-mg twice-daily doses of the CYP3A inhibitor clarithromycin with a single 50-mg abemaciclib dose increased abemaciclib <math>AUC_{0-\infty}</math> and <math>C_{max}</math> by approximately 3.37- and 1.30-fold, respectively, relative to a single 50-mg abemaciclib dose given alone, and the total analytes <math>AUC_{0-\infty}</math> increased by 2.19-fold but <math>C_{max}</math> remained nearly unaffected (ratio 0.93). The abemaciclib dose should be adjusted for patients who cannot avoid CYP3A inhibitors.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Effect of CYP3A Inducers</b>                    | <p>In Study I3Y-MC-JPBF (Study JPBF), rifampin decreased abemaciclib <math>AUC_{0-\infty}</math> and <math>C_{max}</math> approximately by 95% and 92%, respectively. The <math>AUC_{0-\infty}</math> and <math>C_{max}</math> of total analytes decreased by 77% and 45%, respectively, in the presence of rifampin. Concomitant administration of abemaciclib with CYP3A inducers such as rifampin and carbamazepine should be avoided. However, in clinical studies of abemaciclib, the use of dexamethasone, a weak CYP3A inducer, has been allowed.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

## 6.2 MODEL DIAGNOSTICS

**Figure 10: Model diagnostics for the C-QT model described in section 5.3 (abemaciclib)**

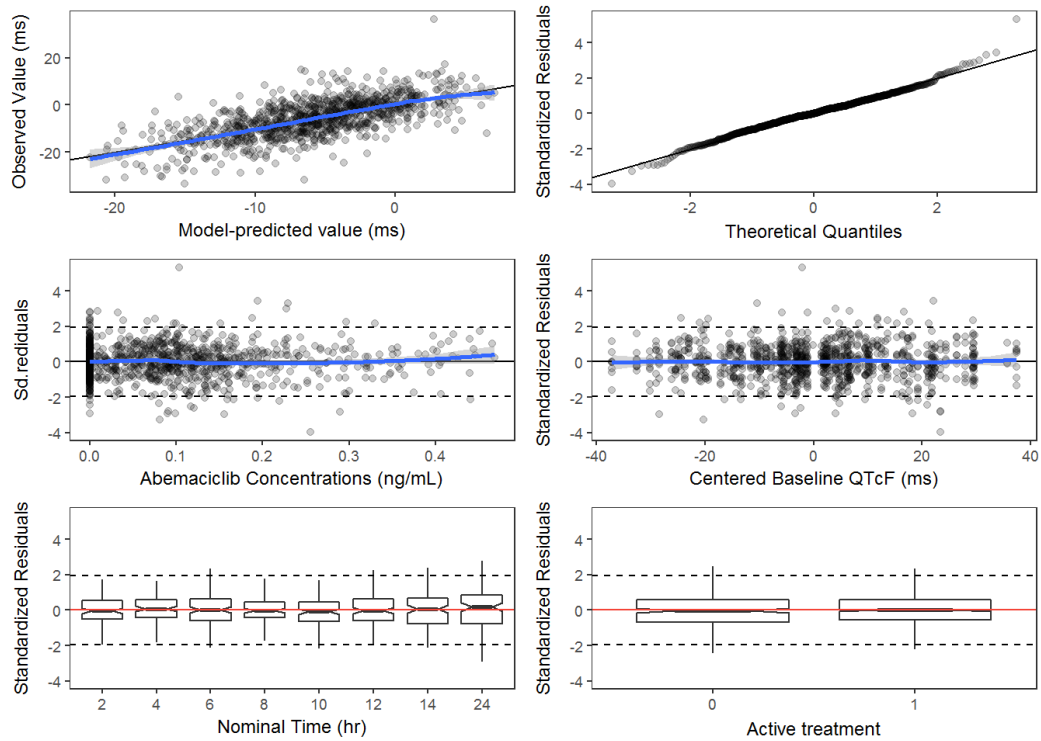


**Figure 11: Model diagnostics for the C-QT model described in section 5.3 (M2)**

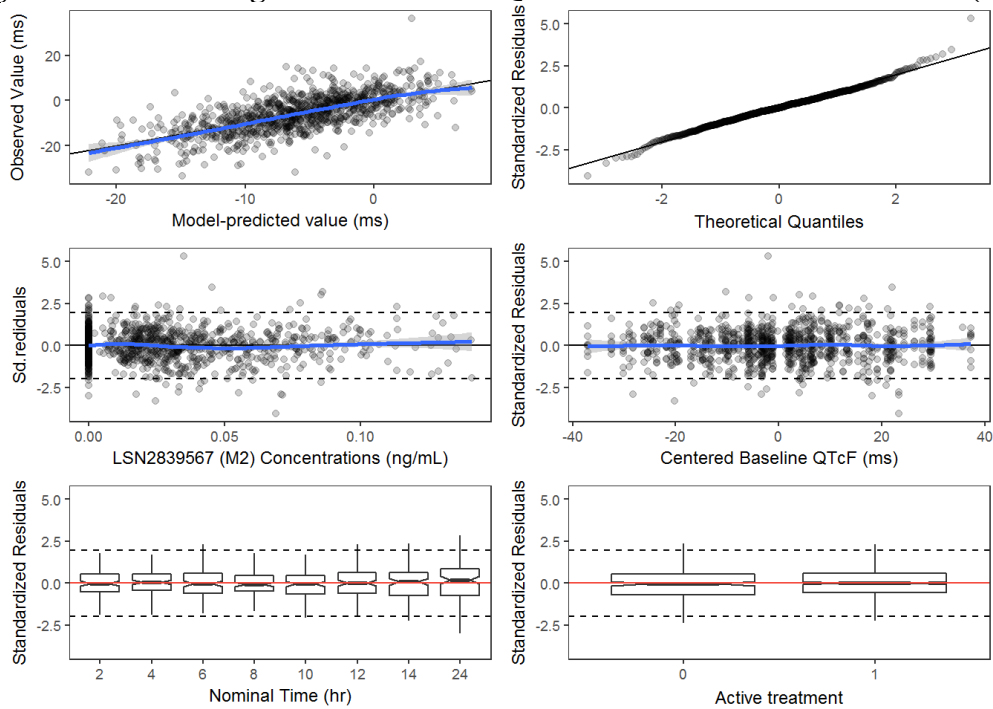
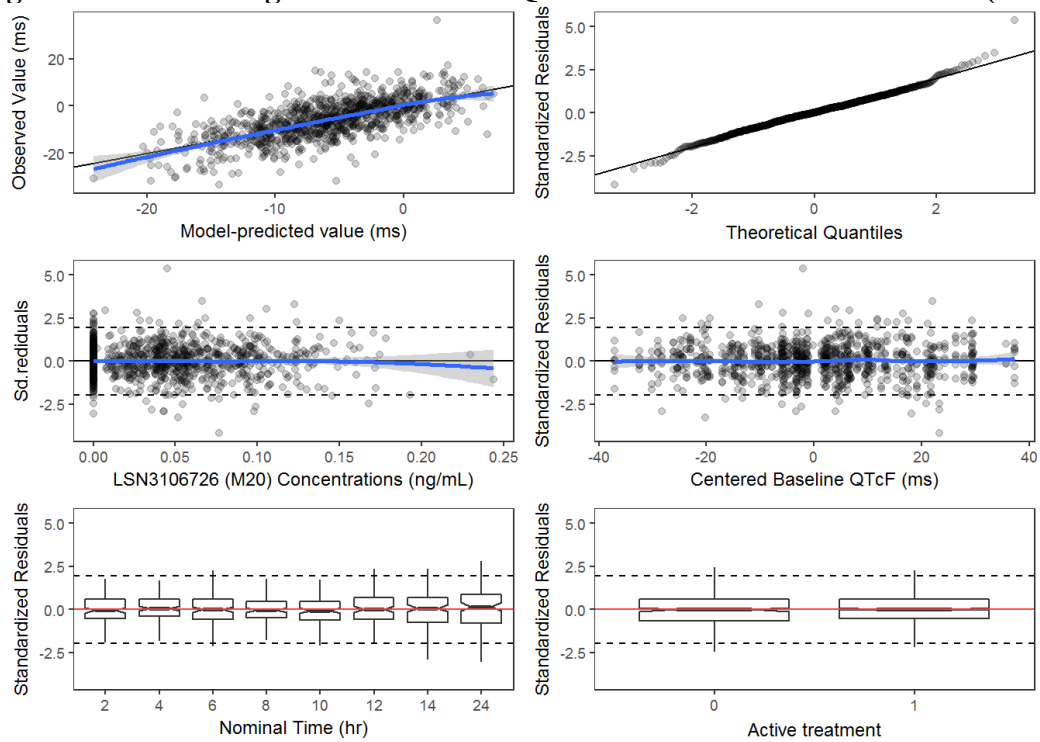


**Figure 12: Model diagnostics for the C-QT model described in section 5.3 (M20)**



### 6.3 PARAMETERS OF CONCENTRATION- $\Delta$ QTcF RELATIONSHIP

**Table 18: Abemaciclib Concentration- $\Delta$ QTcF relationship fixed effects parameter estimates**

| <i>Fixed effect parameter</i> | <i>Estimate</i> | <i>Lower 95% CI</i> | <i>Upper 95% CI</i> | <i>p</i> |
|-------------------------------|-----------------|---------------------|---------------------|----------|
| (Intercept)                   | -6.939008389    | -8.840592646        | -5.037424132        | <0.001   |
| ACTIVE1                       | 1.736235483     | 0.358015105         | 3.114455861         | 0.0136   |
| TIME12                        | 0.694380778     | -0.910858248        | 2.299619804         | 0.396    |
| TIME14                        | 3.363213075     | 1.735942579         | 4.990483572         | <0.001   |
| TIME2                         | 2.912844313     | 1.132362205         | 4.693326421         | 0.00137  |
| TIME24                        | -0.011894486    | -1.635436857        | 1.611647885         | 0.989    |
| TIME4                         | 3.884431924     | 2.220454822         | 5.548409026         | <0.001   |
| TIME6                         | 0.838788968     | -0.774304799        | 2.451882735         | 0.308    |
| TIME8                         | -1.938913402    | -3.543981831        | -0.333844973        | 0.018    |
| QTcF.cBS                      | -0.278456874    | -0.346864966        | -0.210048782        | <0.001   |
| CP                            | -11.70262464    | -21.09123252        | -2.314016772        | 0.0161   |

**Table 19: Abemaciclib Metabolite LSN2839567(M2) Concentration-  $\Delta$  QTcF relationship fixed effects parameter estimates**

| <i>Fixed effect parameter</i> | <i>Estimate</i> | <i>Lower 95% CI</i> | <i>Upper 95% CI</i> | <i>p</i> |
|-------------------------------|-----------------|---------------------|---------------------|----------|
| (Intercept)                   | -7.06251        | -8.95819            | -5.16684            | -13.4545 |
| ACTIVE1                       | 1.670684        | 0.300367            | 3.041002            | 41.77851 |
| TIME12                        | 0.733932        | -0.85922            | 2.327085            | 110.5977 |
| TIME14                        | 3.355763        | 1.739724            | 4.971802            | 24.53617 |
| TIME2                         | 3.311648        | 1.636832            | 4.986465            | 25.76838 |
| TIME24                        | 0.040764        | -1.56833            | 1.649861            | 2011.193 |
| TIME4                         | 4.29018         | 2.689905            | 5.890454            | 19.00498 |
| TIME6                         | 1.08378         | -0.51377            | 2.68133             | 75.10346 |
| TIME8                         | -1.89778        | -3.49221            | -0.30334            | -42.8062 |
| QTcF.cBS                      | -0.2782         | -0.34689            | -0.20951            | -12.4403 |
| CP                            | -36.4412        | -68.7062            | -4.17617            | -43.749  |

**Table 20: Abemaciclib Metabolite LSN3106726(M20) Concentration-  $\Delta$  QTcF relationship fixed effects parameter estimates**

| <i>Fixed effect parameter</i> | <i>Estimate</i> | <i>Lower 95% CI</i> | <i>Upper 95% CI</i> | <i>p</i> |
|-------------------------------|-----------------|---------------------|---------------------|----------|
| (Intercept)                   | -7.04709        | -8.95234            | -5.14184            | -13.5464 |
| ACTIVE1                       | 1.800595        | 0.300079            | 3.301111            | 42.43872 |
| TIME12                        | 0.8106          | -0.78818            | 2.409385            | 100.4919 |
| TIME14                        | 3.540736        | 1.921763            | 5.159708            | 23.29681 |
| TIME2                         | 3.087954        | 1.330274            | 4.845634            | 29.00293 |
| TIME24                        | 0.519199        | -1.08547            | 2.123866            | 157.4713 |

|          |          |          |          |          |
|----------|----------|----------|----------|----------|
| TIME4    | 3.971947 | 2.321709 | 5.622185 | 21.16917 |
| TIME6    | 0.784898 | -0.82437 | 2.394169 | 104.4638 |
| TIME8    | -2.00033 | -3.59921 | -0.40144 | -40.7253 |
| QTCF.cBS | -0.2781  | -0.34647 | -0.20973 | -12.3874 |
| CP       | -25.7968 | -48.3886 | -3.20496 | -43.7781 |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LARS JOHANNESSEN

07/18/2017

Yuan Xu was the primary reviewer.

YUAN XU

07/18/2017

EIJI ISHIDA

07/18/2017

MOHAMMAD A RAHMAN

07/18/2017

MICHAEL Y LI

07/18/2017

CHRISTINE E GARNETT

07/18/2017

# RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA # 208716<br>BLA#                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | NDA Supplement #: S-<br>BLA Supplement #: S- | Efficacy Supplement Category:<br><input type="checkbox"/> New Indication (SE1)<br><input type="checkbox"/> New Dosing Regimen (SE2)<br><input type="checkbox"/> New Route Of Administration (SE3)<br><input type="checkbox"/> Comparative Efficacy Claim (SE4)<br><input type="checkbox"/> New Patient Population (SE5)<br><input type="checkbox"/> Rx To OTC Switch (SE6)<br><input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7)<br><input type="checkbox"/> Labeling Change With Clinical Data (SE8)<br><input type="checkbox"/> Manufacturing Change With Clinical Data (SE9)<br><input type="checkbox"/> Animal Rule Confirmatory Study (SE10) |
| Proprietary Name: Verzenio<br>Established/Proper Name: abemaciclib<br>Dosage Form: tablet<br>Strengths: 50 mg, 100 mg, 150 mg, 200 mg<br>Route(s) of Administration: oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Applicant: Eli Lilly<br>Agent for Applicant (if applicable):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Date of Application: May 5, 2017<br>Date of Receipt: May 5, 2017<br>Date clock started after Unacceptable for Filing (UN):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| PDUFA/BsUFA Goal Date: January 5, 2018                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                              | Action Goal Date (if different): September 29, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Filing Date: July 4, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                              | Date of Filing Meeting: June 7, 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Chemical Classification (original NDAs only) :<br><input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination<br><input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination<br><input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination<br><input type="checkbox"/> Type 4- New Combination<br><input type="checkbox"/> Type 5- New Formulation or New Manufacturer<br><input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA<br><input type="checkbox"/> Type 8- Partial Rx to OTC Switch<br><input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)<br><input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval) |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Proposed indication(s)/Proposed change(s): <span style="float: right;">(b) (4)</span><br><div style="background-color: #cccccc; height: 50px; width: 100%;"></div> <span style="float: right;">(b) (4)</span>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Type of Original NDA: NME Type 1<br>AND (if applicable)<br>Type of NDA Supplement:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                              | <input checked="" type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| Type of BLA<br><br><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> 351(a)<br><input type="checkbox"/> 351(k)                                                                                                                                                                                                                                                                                                                                                                                 |    |         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|---------|
| Review Classification:<br><br><i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <li>• <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></li> <li>• <i>The product is a Qualified Infectious Disease Product (QIDP)</i></li> <li>• <i>A Tropical Disease Priority Review Voucher was submitted</i></li> <li>• <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li> </ul> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> Standard<br><input checked="" type="checkbox"/> Priority<br><br><input type="checkbox"/> Pediatric WR<br><input type="checkbox"/> QIDP<br><input type="checkbox"/> Tropical Disease Priority Review Voucher<br><input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher                                                                                                                                    |    |         |
| Resubmission after withdrawal? <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Resubmission after refuse to file? <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                        |    |         |
| Part 3 Combination Product? <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/> Convenience kit/Co-package<br><input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Device coated/impregnated/combined with drug<br><input type="checkbox"/> Device coated/impregnated/combined with biologic<br><input type="checkbox"/> Separate products requiring cross-labeling<br><input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Possible combination based on cross-labeling of separate products<br><input type="checkbox"/> Other (drug/device/biological product) |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |         |
| <input checked="" type="checkbox"/> Fast Track Designation<br><input checked="" type="checkbox"/> Breakthrough Therapy Designation<br><i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i><br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other:                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |    |         |
| Collaborative Review Division (if OTC product):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |         |
| List referenced IND Number(s): 106100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |         |
| Goal Dates/Product Names/Classification Properties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | YES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | NO                                                                                                                                                                                                                                                                                                                                                                                                                                                 | NA | Comment |
| PDUFA/BsUFA and Action Goal dates correct in the electronic archive?<br><br><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>                                                                                                                                                                                                                                                                                                                                                                           | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                           |    |         |
| Are the established/proper and applicant names correct in electronic archive?<br><br><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                           |    |         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                            |                                     |                          |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|----------------|
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a><br><br><i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                        | <input type="checkbox"/>            | <input type="checkbox"/> |                |
| <b>Application Integrity Policy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                 | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i><br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>                                                                                                                                                                                                                                                                                             | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> |                          |                |
| If yes, explain in comment column.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                            |                                     |                          |                |
| If affected by AIP, has OC been notified of the submission?<br>If yes, date notified:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>            |                          |                |
| <b>User Fees</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                 | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                        | <input type="checkbox"/>            |                          |                |
| <u>User Fee Status</u><br><br><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>                                                                                                                                                                                                                                                                                           | Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):<br><br><input checked="" type="checkbox"/> Paid<br><input type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> Not required |                                     |                          |                |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>                                                                                                                                                                                                                                                                                                        | Payment of other user fees:<br><br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears                                                                                                                                                                                                                               |                                     |                          |                |
| <u>User Fee Bundling Policy</u><br><br><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i><br><a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>                                                                                                                                                                           | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i><br><br><input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                                                                                                                                  |                                     |                          |                |
| <b>505(b)(2)<br/>(NDAs/NDA Efficacy Supplements only)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                 | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes</b> , answer the bulleted questions below:                                                                                                                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>            |                          |                |
| • Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>            |                          |                |

| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <input type="checkbox"/> | <input type="checkbox"/> |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--------------------------|--------------------------|--|--|
| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <input type="checkbox"/> | <input type="checkbox"/> |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
| <ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b><br/> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Application No.          | Drug Name                | Exclusivity Code       | Exclusivity Expiration |  |  |  |  |  |  |  |  |  |  |  |  | <input type="checkbox"/> | <input type="checkbox"/> |  |  |
| Application No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Drug Name                | Exclusivity Code         | Exclusivity Expiration |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
| <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                          |                          |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |
| <ul style="list-style-type: none"> <li>If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?</li> </ul> <p><b>Check the Electronic Orange Book at:</b><br/> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If no, include template language in the 74-day letter.</b></p> <p><b>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</b></p> <p><b>Note: Pharmaceutical equivalents</b> are drug products in identical dosage forms and route(s) of administration that: <b>(1)</b> contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; <b>(2)</b> do not necessarily contain the same inactive ingredients; <b>and (3)</b> meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</p> | <input type="checkbox"/> | <input type="checkbox"/> |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |                          |                          |  |  |

| Exclusivity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | YES                                 | NO                                  | NA                                  | Comment |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|---------|
| Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b><br><a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>                                                                                                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |         |
| <b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?<br><br><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>                                                                                                                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |         |
| <b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?<br><br><b>If yes, # years requested:</b> 5<br><br><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>                                                                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> | <input type="checkbox"/>            | <input type="checkbox"/>            |         |
| <b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/>            | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |         |
| <b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?<br><br><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>                                                                                                                                                                                                                                                                                             | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |         |
| <b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?<br><br><i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i><br><br><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |         |

| Format and Content                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|-------------------------------------|----------------|
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> All paper (except for COL)<br><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br><input checked="" type="checkbox"/> CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD) |                          |                                     |                |
| <p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
| <b>Overall Format/Content</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>YES</b>                                                                                                                                                                                                                                                                                        | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| <p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup><br/> <b>If not</b>, explain (e.g., waiver granted).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                               | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> |                                     |                |
| <p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible<br/> <input checked="" type="checkbox"/> English (or translated into English)<br/> <input checked="" type="checkbox"/> pagination<br/> <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no</b>, explain.</p>                                                                           | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> |                                     |                |
| <p><b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes</b>, BLA #</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>                                                                                                                                                                                                                                                                          | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
| <b>Forms and Certifications</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
| <p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included.</i></p> <p><b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</p> |                                                                                                                                                                                                                                                                                                   |                          |                                     |                |
| <b>Application Form</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>YES</b>                                                                                                                                                                                                                                                                                        | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| <p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>                                                                                                                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> |                                     |                |
| <p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                               | <input type="checkbox"/> | <input type="checkbox"/>            |                |

<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

| <b>Patent Information<br/>(NDAs/NDA efficacy supplements only)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|----------------|
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>Financial Disclosure</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?<br><br><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i><br><br><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <b>Clinical Trials Database</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Is form FDA 3674 included with authorized signature?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i><br><br><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>                                                                                                                                                                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <b>Debarment Certification</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Is a correctly worded Debarment Certification included with authorized signature?<br><br><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i><br><br><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>Field Copy Certification<br/>(NDAs/NDA efficacy supplements only)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| <b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?<br><br><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i><br><br><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |

| Controlled Substance/Product with Abuse Potential                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | YES                                 | NO                                  | NA                                  | Comment |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|---------|
| <p>For NMEs:<br/>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs:<br/><i>Date of consult sent to Controlled Substance Staff:</i></p>                                                                                                                                                                                                                                                                                            | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |         |
| Pediatrics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | YES                                 | NO                                  | NA                                  | Comment |
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |                                     |         |
| <p><b>If the application triggers PREA</b>, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> | <input type="checkbox"/>            | <input type="checkbox"/>            |         |
| <p><b>If required by the agreed iPSP</b>, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>                                                                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |         |
| <p><b><u>BPCA:</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required<sup>3</sup></i></p>                                                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |         |

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

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| <b>Proprietary Name</b>                                                                                                                                                                                                                                                                                                                                                                                                | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>NO</b>                                                    | <b>NA</b>                                                    | <b>Comment</b> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|----------------|
| Is a proposed proprietary name submitted?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>                                                                                                                                                                                                                                | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>                                     | <input type="checkbox"/>                                     |                |
| <b>REMS</b>                                                                                                                                                                                                                                                                                                                                                                                                            | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>NO</b>                                                    | <b>NA</b>                                                    | <b>Comment</b> |
| Is a REMS submitted?<br><br><i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>                                                                                                                                                                                                                                                                                          | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/>                          | <input type="checkbox"/>                                     |                |
| <b>Prescription Labeling</b>                                                                                                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/> <b>Not applicable</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                              |                                                              |                |
| Check all types of labeling submitted.                                                                                                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI)<br><input checked="" type="checkbox"/> Patient Package Insert (PPI)<br><input type="checkbox"/> Instructions for Use (IFU)<br><input type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labeling<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent labeling<br><input type="checkbox"/> Other (specify) |                                                              |                                                              |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>NO</b>                                                    | <b>NA</b>                                                    | <b>Comment</b> |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br><i>If no, request applicant to submit SPL before the filing date.</i>                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>                                     |                                                              |                |
| Is the PI submitted in Physician Labeling Rule (PLR) format? <sup>4</sup>                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/>                                     |                                                              |                |
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>                                                                   | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                     | <input checked="" type="checkbox"/>                          |                |
| <b>For applications submitted on or after June 30, 2015:</b><br>Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?<br><br>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?                                                                                                                             | <input checked="" type="checkbox"/><br><br><br><input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/><br><br><br><input type="checkbox"/> | <input type="checkbox"/><br><br><br><input type="checkbox"/> |                |
| <b>For applications submitted on or after June 30, 2015:</b><br><b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i> | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/>                                     | <input checked="" type="checkbox"/>                          |                |

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

|                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|----------------|
| Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?                                                                                                                 | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> | <input type="checkbox"/> |                |
| Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )                                                                                                                         | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> | <input type="checkbox"/> |                |
| Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?                                           | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>OTC Labeling</b>                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> <b>Not Applicable</b>                                                                                                                                                                                                                                                                                                                                        |                          |                          |                |
| Check all types of labeling submitted.                                                                                                                                                                                                          | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify) |                          |                          |                |
|                                                                                                                                                                                                                                                 | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                       | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Is electronic content of labeling (COL) submitted?                                                                                                                                                                                              | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> |                          |                |
| <i>If no, request in 74-day letter.</i>                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                |
| Are annotated specifications submitted for all stock keeping units (SKUs)?                                                                                                                                                                      | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <i>If no, request in 74-day letter.</i>                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                |
| If representative labeling is submitted, are all represented SKUs defined?                                                                                                                                                                      | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <i>If no, request in 74-day letter.</i>                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                          |                |
| All labeling/packaging sent to OSE/DMEPA?                                                                                                                                                                                                       | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Other Consults</b>                                                                                                                                                                                                                           | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                       | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)<br><i>If yes, specify consult(s) and date(s) sent:</i><br>QT 5/11/2017, DMPP 5/31/2017, OSI 5/26/2017, DMEPA 5/17/2017, OPDP 5/17/2017 | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Meeting Minutes/SPAs</b>                                                                                                                                                                                                                     | <b>YES</b>                                                                                                                                                                                                                                                                                                                                                                                       | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| End-of Phase 2 meeting(s)?<br><b>Date(s):</b> August 24, 2015                                                                                                                                                                                   | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> |                          |                |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> March 1, 2016, May 9, 2017                                                                                                                                                        | <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> |                          |                |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b>                                                                                                                                                                                     | <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                         | X                        |                          |                |

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APPEARS THIS WAY ON ORIGINAL

# ATTACHMENT

## MEMO OF FILING MEETING

**DATE:** June 7, 2017

**BACKGROUND:** Eli Lilly has submitted a new NDA 208716 for abemaciclib (b) (4)

and is requesting priority review. The associated IND 106100 received breakthrough therapy designation. This application was submitted on May 5, 2017 and final proposed labeling will be provided on or before July 5, 2017 and will include complete MONARCH 2 labeling as well as the newly completed clinical pharmacology study, JPCK. Eli Lilly will also submit updated Module 2 summary document that include MONARCH 2 study and related information no later than July 5, 2017

### REVIEW TEAM:

| Discipline/Organization                            | Names                     |                        | Present at filing meeting? (Y or N) |
|----------------------------------------------------|---------------------------|------------------------|-------------------------------------|
| Regulatory Project Management                      | RPM:                      | Janice Kim             | Y                                   |
|                                                    | CPMS/TL:                  | Alice Kacuba           | N                                   |
| Cross-Discipline Team Leader (CDTL)                | Laleh Amiri-Kordestani    |                        | Y                                   |
| Division Director/Deputy                           | Julia Beaver/Amna Ibrahim |                        | Y                                   |
| Office Director/Deputy                             | Richard Pazdur            |                        | N                                   |
| Clinical                                           | Reviewer:                 | Lynn Howie             | Y                                   |
|                                                    | TL:                       | Laleh Amiri Kordestani | Y                                   |
| Social Scientist Review (for OTC products)         | Reviewer:                 | N/A                    |                                     |
|                                                    | TL:                       | N/A                    |                                     |
| OTC Labeling Review (for OTC products)             | Reviewer:                 | N/A                    |                                     |
|                                                    | TL:                       | N/A                    |                                     |
| Clinical Microbiology (for antimicrobial products) | Reviewer:                 | N/A                    |                                     |
|                                                    | TL:                       | N/A                    |                                     |
| Clinical Pharmacology                              | Reviewer:                 | Vadryn Pierre          | Y                                   |

|                   |           |                          |   |
|-------------------|-----------|--------------------------|---|
|                   | TL:       | Jeanne Fourie Zirkelbach | Y |
| • Genomics        | Reviewer: | Ruby Leong               | N |
| • Pharmacometrics | Reviewer: | Nan Zheng                | Y |
| Biostatistics     | Reviewer: | Erik Bloomquist          | Y |
|                   | TL:       | Shenghui Tang            | Y |

|                                                                            |                                                    |                        |   |
|----------------------------------------------------------------------------|----------------------------------------------------|------------------------|---|
| Nonclinical Pharmacology/Toxicology)                                       | Reviewer:                                          | Tiffany Ricks          | Y |
|                                                                            | TL:                                                | Todd Palmby            | Y |
| Statistics (carcinogenicity)                                               | Reviewer:                                          | N/A                    |   |
|                                                                            | TL:                                                | N/A                    |   |
| Product Quality (CMC) Review Team:                                         | ATL:                                               | Xiao Chen              | Y |
|                                                                            | RBPM:                                              | Kristine Leahy         | N |
| • Drug Substance                                                           | Reviewer:                                          | Sithamali Chandramouli | Y |
| • Drug Product                                                             | Reviewer:                                          | Olen Stephens          | Y |
| • Process                                                                  | Reviewer:                                          | Ying Zhang             | Y |
| • Microbiology                                                             | Reviewer:                                          | N/A                    |   |
| • Facility                                                                 | Reviewer:                                          | Krisnakali Ghosh       | Y |
| • Biopharmaceutics                                                         | Reviewer:                                          | Banu Zolnik            | N |
| • Immunogenicity                                                           | Reviewer:                                          | N/A                    |   |
| • Labeling (BLAs only)                                                     | Reviewer:                                          | N/A                    |   |
| • Other (e.g., Branch Chiefs, EA Reviewer)                                 | EA – James Laurensen, ETT – Tom O’Connor/Larry Lee |                        | Y |
| OMP/OMPI/DMPP (MedGuide, PPI, IFU)                                         | Reviewer:                                          | Shawna Hutchins        | N |
|                                                                            | TL:                                                | Barbara Fuller         | N |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling) | Reviewer:                                          | Kevin Wright           | Y |
|                                                                            | TL:                                                | N/A                    |   |
| OSE/DMEPA (proprietary name, carton/container labeling)                    | Reviewer:                                          | Alice Tu               | Y |
|                                                                            | TL:                                                | Grace Jones            | N |
| OSE/DRISK (REMS)                                                           | Reviewer:                                          | Ingrid Chapman         | N |
|                                                                            | TL:                                                | Elizabeth Everhart     | Y |
| OC/OSI/DSC/PMSB (REMS)                                                     | Reviewer:                                          | N/A                    |   |
|                                                                            | TL:                                                | N/A                    |   |

|                                                                                                                                                                                               |           |                |   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------|---|
| Bioresearch Monitoring (OSI)                                                                                                                                                                  | Reviewer: | Sharon Gershon | Y |
|                                                                                                                                                                                               | TL:       | Susan Thompson | N |
| Controlled Substance Staff (CSS)                                                                                                                                                              | Reviewer: | N/A            |   |
|                                                                                                                                                                                               | TL:       | N/A            |   |
| Other reviewers/disciplines                                                                                                                                                                   |           |                |   |
| <ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p><small>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</small></p> | Reviewer: |                |   |
|                                                                                                                                                                                               | TL:       |                |   |
| Other attendees                                                                                                                                                                               |           |                |   |
|                                                                                                                                                                                               |           |                |   |
|                                                                                                                                                                                               |           |                |   |
|                                                                                                                                                                                               |           |                |   |
| <small>*For additional lines, right click here and select "insert rows below"</small>                                                                                                         |           |                |   |

### **FILING MEETING DISCUSSION:**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                    |
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| <b>GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                    |
| <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> </li> </ul> | <input checked="" type="checkbox"/> Not Applicable<br><br><input type="checkbox"/> YES <input type="checkbox"/> NO<br><br><input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                             |
| <ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> No comments                                                                                         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLINICAL</b><br><br><b>Comments:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter                           |
| <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> | <input type="checkbox"/> YES<br>Date if known:<br><input checked="" type="checkbox"/> NO<br><input type="checkbox"/> To be determined<br><br>Reason: The application did not raise significant safety or efficacy issues |
| <ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                        |
| <b>CONTROLLED SUBSTANCE STAFF</b> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter                           |
| <b>CLINICAL MICROBIOLOGY</b><br><br><b>Comments:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter                           |

|                                                                                                                                                                                                                                       |                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLINICAL PHARMACOLOGY</b><br><br><b>Comments:</b>                                                                                                                                                                                  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>                                                                                                                          | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO                                                                                                                         |
| <b>BIOSTATISTICS</b><br><br><b>Comments:</b>                                                                                                                                                                                          | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <b>NONCLINICAL<br/>(PHARMACOLOGY/TOXICOLOGY)</b><br><br><b>Comments:</b>                                                                                                                                                              | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <b>PRODUCT QUALITY (CMC)</b><br><br><b>Comments:</b>                                                                                                                                                                                  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <b><u>New Molecular Entity (NDAs only)</u></b><br><br><ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>                                                                                                        | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                         |
| <b><u>Environmental Assessment</u></b><br><br><ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no, was a complete EA submitted?</b></p> <b>Comments:</b> | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input type="checkbox"/> YES<br><input type="checkbox"/> NO                                                      |
| <b><u>Facility Inspection</u></b><br><br><ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <b>Comments:</b>                                                                                    | <input type="checkbox"/> Not Applicable<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><u>Facility/Microbiology Review (BLAs only)</u></b><br><br><b>Comments:</b>                                                                                                                                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <b><u>CMC Labeling Review (BLAs only)</u></b><br><br><b>Comments:</b>                                                                                                                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/> Review issues for 74-day letter                                                                                                                                       |
| <b><u>APPLICATIONS IN THE PROGRAM (PDUFA V)<br/>(NME NDAs/Original BLAs)</u></b><br><br><ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul> | <input type="checkbox"/> N/A<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO       |
| <ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>                                                                                                                                                                                                                                                                                                                                                   | Module 2 components (agreed to during Pre-NDA meeting)                                                                                                                                         |
| <ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                         |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>                                                                                                                                                                                                                                                                                                      | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                         |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO                                                                                                                         |

| REGULATORY PROJECT MANAGEMENT                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Signatory Authority:</b> Richard Pazdur, MD<br><br><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): July 25, 2017<br><br><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):<br><br><b>Comments:</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| REGULATORY CONCLUSIONS/DEFICIENCIES                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <input type="checkbox"/>                                                                                                                                                                                                                                                                                    | The application is unsuitable for filing. Explain why:                                                                                                                                                                                                                                                                                                                                                                                  |
| <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                         | The application, on its face, appears to be suitable for filing.<br><br><u>Review Issues:</u><br><br><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.<br><input type="checkbox"/> Review issues have been identified for the 74-day letter.<br><br><u>Review Classification:</u><br><br><input type="checkbox"/> Standard Review<br><input checked="" type="checkbox"/> Priority Review |
| ACTION ITEMS                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                         | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).                                                                                                                                                                                                                        |
| <input type="checkbox"/>                                                                                                                                                                                                                                                                                    | If RTF, notify everyone who already received a consult request, OSE PM, and RBPM                                                                                                                                                                                                                                                                                                                                                        |
| <input type="checkbox"/>                                                                                                                                                                                                                                                                                    | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                         | If priority review, notify applicant in writing by day 60 (see CST for choices)                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                         | Send review issues/no review issues by day 74                                                                                                                                                                                                                                                                                                                                                                                           |
| <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                         | Conduct a PLR format labeling review and include labeling issues in the 74-day letter                                                                                                                                                                                                                                                                                                                                                   |
| <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                         | Update the PDUFA V DARRTS page (for applications in the Program)                                                                                                                                                                                                                                                                                                                                                                        |
| <input type="checkbox"/>                                                                                                                                                                                                                                                                                    | Other                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Annual review of template by OND ADRAAs completed: April 2016

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE H KIM  
07/11/2017

ALICE KACUBA  
07/12/2017