CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021344Orig1s026

Trade Name: **Faslodex Injection**

Generic Name: **fulvestrant**

Sponsor: **AstraZeneca Pharmaceuticals LP**

Approval Date: 03/02/2016

Indications: FASLODEX is an estrogen receptor antagonist indicated for the:

- Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
- Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344/S-026

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Elinore Mercer, PhD
Director Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Mercer:

Please refer to your Supplemental New Drug Application (sNDA) dated November 17, 2015, received November 17, 201, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Faslodex® Injection (fulvestrant) Solution for Injection 250 mg/5 mL.

This Prior Approval supplemental new drug application provides for Faslodex® (fulvestrant) Solution for Injection as indicated for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert and patient package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease does not exist in children.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
03/02/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FASLODEX safely and effectively. See full prescribing information for FASLODEX.

FASLODEX® (fulvestrant) injection, for intramuscular use
Initial U.S. Approval: 2002

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	03/2016
Dosage and Administration (2.1, 2.2, 2.3)	03/2016
Warnings and Precautions (5.3)	03/2016

---------- INDICATIONS AND USAGE ----------

FASLODEX is an estrogen receptor antagonist indicated for the:

- Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. (1)
- Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- FASLODEX 500 mg should be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. (2.1, 14)
- A dose of 250 mg is recommended in patients with moderate hepatic impairment to be administered intramuscularly into the buttock slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter. (2.2, 5.2, 8.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

FASLODEX, an injection for intramuscular administration, is supplied as 50 mg/mL fulvestrant. (3)

---------- CONTRAINDICATIONS ----------

- Hypersensitivity. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Bleeding: Use with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. (5.1)
- Increased Exposure in Patients with Hepatic Impairment: Use a 250 mg dose for patients with moderate hepatic impairment. (2 2, 5.2, 8.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

- The most common adverse reactions occurring in ≥5% of patients receiving FASLODEX 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. (6.1)
- Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of FASLODEX patients and were not dose-dependent. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- There are no known drug-drug interactions. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Advise not to breast-feed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Monotherapy

FASLODEX is indicated for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

Combination Therapy with Palbociclib

FASLODEX is indicated for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Monotherapy

The recommended dose is 500 mg to be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter *[see Clinical Studies (14)].*

Combination Therapy with Palbociclib

When FASLODEX is used in combination with palbociclib, the recommended dose is 500 mg to be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. The recommended dose of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food. Please refer to the full prescribing information of palbociclib.

Pre/perimenopausal women treated with the combination FASLODEX plus palbociclib should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards *[see Clinical Studies (14)]*.

2.2 Dose Modification

Monotherapy

Hepatic Impairment:

A dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered intramuscularly into the buttock slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter.

FASLODEX has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

Combination Therapy with Palbociclib

When FASLODEX is used in combination with palbociclib, refer to monotherapy dose modification instructions for FASLODEX. Refer to the full prescribing information of palbociclib for its dose modification, management of toxicities, and for use with concomitant medication.

2.3 Administration Technique

The proper method of administration of FASLODEX for intramuscular use is described in the instructions that follow:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
3. Peel open the safety needle (SafetyGlide™) outer packaging. For complete SafetyGlide™ instructions refer below to the "Directions for Use of SafetyGlide™".
4. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap (see Figure 1).
5. Twist to lock the needle to the luer connector.
6. Remove needle sheath.
7. Remove excess gas from the syringe (a small gas bubble may remain).
8. Administer intramuscularly into the buttock slowly.
9. Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered (see Figure 2).
10. Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector.
11. Repeat steps 1 through 10 for second syringe.

How To Use FASLODEX

For the 2 x 5 mL syringe package, the contents of both syringes must be injected to receive the 500 mg recommended dose.

SAFETYGLIDE™ INSTRUCTIONS FROM BECTON DICKINSON

SafetyGlide™ is a trademark of Becton Dickinson and Company.

Important Administration Information

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure. Hands must remain behind the needle at all times during use and disposal.

Do not autoclave SafetyGlide™ Needle before use.

Parenteral drug products should be visually inspected for any particulate matter and discoloration prior to administration, whenever solution and container permit.

DIRECTIONS FOR USE OF SAFETYGLIDE™

For each syringe:

Remove glass syringe barrel from tray and check that it is not damaged.

Peel apart packaging of the SafetyGlide™, break the seal of the white plastic cover on the syringe Luer connector and attach the SafetyGlide™ needle to the Luer Lock of the syringe by twisting.

Transport filled syringe to point of administration.

Pull shield straight off needle to avoid damaging needle point.

Administer injection following package instruction.

For user convenience, the needle 'bevel up' position is orientated to the lever arm, as shown in Figure 3.

Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered (Figure 2).

Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector.

Activation of the protective mechanism may cause minimal splatter of fluid that may remain on the needle after injection.

For greatest safety, use a one-handed technique and activate away from self and others.

After single use, discard in an approved sharps collector in accordance with applicable regulations and institutional policy.

Becton Dickinson guarantees the contents of their unopened or undamaged packages to be sterile, non-toxic and non-pyrogenic.

Figure 1

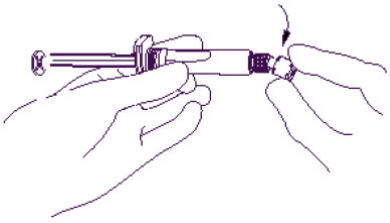


Figure 2

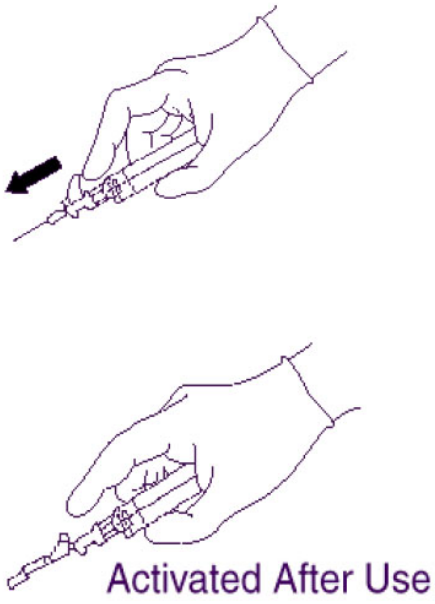
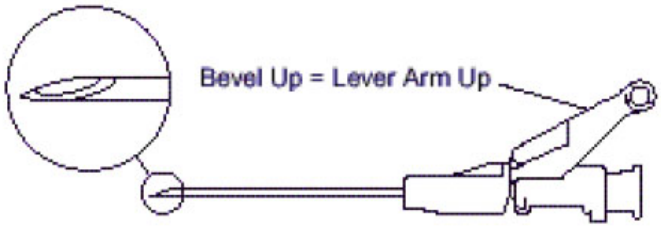


Figure 3



3 DOSAGE FORMS AND STRENGTHS

FASLODEX, an injection for intramuscular administration, is supplied as 5-mL prefilled syringes containing 50 mg/mL fulvestrant.

4 CONTRAINDICATIONS

FASLODEX is contraindicated in patients with a known hypersensitivity to the drug or to any of its components. Hypersensitivity reactions, including urticaria and angioedema, have been reported in association with FASLODEX *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

Because FASLODEX is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

5.2 Increased Exposure in Patients with Hepatic Impairment

The safety and pharmacokinetics of FASLODEX were evaluated in a study in seven subjects with moderate hepatic impairment (Child-Pugh class B) and seven subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose of 250 mg is recommended *[see Dosage and Administration (2.2)].*

FASLODEX has not been studied in patients with severe hepatic impairment (Child-Pugh class C) *[see Use in Specific Populations (8.6)]*.

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, FASLODEX can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fulvestrant to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at daily doses that are significantly less than the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with FASLODEX and for one year after the last dose *[see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Risk of Bleeding *[see Warnings and Precautions (5.1)]*
- Increased Exposure in Patients with Hepatic Impairment *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Monotherapy

Comparison of FASLODEX 500 mg and FASLODEX 250 mg

The following adverse reactions (ARs) were calculated based on the safety analysis of Study 1 comparing the administration of FASLODEX 500 mg intramuscularly once a month with FASLODEX 250 mg intramuscularly once a month. The most frequently reported adverse reactions in the fulvestrant 500 mg group were injection site pain (11.6% of patients), nausea (9.7% of patients) and bone pain (9.4% of patients); the most frequently reported adverse reactions in the fulvestrant 250 mg group were nausea (13.6% of patients), back pain (10.7% of patients) and injection site pain (9.1% of patients).

Table 1 lists adverse reactions reported with an incidence of 5% or greater, regardless of assessed causality, from Study 1.

Table 1: Adverse Reactions in Study 1 (≥5% in Either Treatment Group)

Body System and Adverse Reaction	Number (%) of Patients	
	Fulvestrant 500 mg N=361	Fulvestrant 250 mg N=374
Body as a Whole		
Injection Site Pain	42 (11.6)	34 (9.1)
Headache	28 (7.8)	25 (6.7)
Back Pain	27 (7.5)	40 (10.7)
Fatigue	27 (7.5)	24 (6.4)
Pain in Extremity	25 (6.9)	26 (7.0)
Asthenia	21 (5.8)	23 (6.1)
Vascular System		
Hot Flash	24 (6.6)	22 (5.9)
Digestive System		
Nausea	35 (9.7)	51 (13.6)
Vomiting	22 (6.1)	21 (5.6)
Anorexia	22 (6.1)	14 (3.7)
Constipation	18 (5.0)	13 (3.5)
Musculoskeletal System		
Bone Pain	34 (9.4)	28 (7.5)
Arthralgia	29 (8.0)	29 (7.8)
Musculoskeletal Pain	20 (5.5)	12 (3.2)
Respiratory System		
Cough	19 (5.3)	20 (5.3)
Dyspnea	16 (4.4)	19 (5.1)

In the pooled safety population (N=1127) from clinical trials comparing FASLODEX 500 mg to FASLODEX 250 mg, post-baseline increases of ≥1 CTC grade in either AST, ALT, or alkaline phosphatase were observed in >15% of patients receiving FASLODEX. Grade 3-4 increases were observed in 1-2% of patients. The incidence and severity of increased hepatic enzymes (ALT, AST, ALP) did not differ between the 250 mg and the 500 mg FASLODEX arms.

Comparison of FASLODEX 250 mg and Anastrozole 1 mg in Combined Trials (Studies 2 and 3)

The most commonly reported adverse reactions in the FASLODEX and anastrozole treatment groups were gastrointestinal symptoms (including nausea, vomiting, constipation, diarrhea and abdominal pain), headache, back pain, vasodilatation (hot flashes), and pharyngitis.

Injection site reactions with mild transient pain and inflammation were seen with FASLODEX and occurred in 7% of patients (1% of treatments) given the single 5 mL injection (predominantly European Trial Study 3) and in 27% of patients (4.6% of treatments) given the 2 x 2.5 mL injections (North American Trial Study 2).

Table 2 lists adverse reactions reported with an incidence of 5% or greater, regardless of assessed causality, from the two controlled clinical trials comparing the administration of FASLODEX 250 mg intramuscularly once a month with anastrozole 1 mg orally once a day.

Table 2: Adverse Reactions in Studies 2 and 3 (≥5% from Combined Data)

Body System and Adverse Reaction	FASLODEX 250 mg N=423 (%)	Anastrozole 1 mg N=423 (%)
Body as a Whole	68.3	67.6
Asthenia	22.7	27.0
Pain	18.9	20.3
Headache	15.4	16.8
Back Pain	14.4	13.2
Abdominal Pain	11.8	11.6
Injection Site Pain[1]	10.9	6.6
Pelvic Pain	9.9	9.0
Chest Pain	7.1	5.0
Flu Syndrome	7.1	6.4
Fever	6.4	6.4
Accidental Injury	4.5	5.7
Cardiovascular System	30.3	27.9
Vasodilatation	17.7	17.3
Digestive System	51.5	48.0
Nausea	26.0	25.3
Vomiting	13.0	11.8
Constipation	12.5	10.6
Diarrhea	12.3	12.8
Anorexia	9.0	10.9
Hemic and Lymphatic Systems	13.7	13.5
Anemia	4.5	5.0
Metabolic and Nutritional Disorders	18.2	17.7
Peripheral Edema	9.0	10.2
Musculoskeletal System	25.5	27.9
Bone Pain	15.8	13.7
Arthritis	2.8	6.1
Nervous System	34.3	33.8
Dizziness	6.9	6.6
Insomnia	6.9	8.5
Paresthesia	6.4	7.6
Depression	5.7	6.9
Anxiety	5.0	3.8
Respiratory System	38.5	33.6
Pharyngitis	16.1	11.6
Dyspnea	14.9	12.3
Cough Increased	10.4	10.4
Skin and Appendages	22.2	23.4
Rash	7.3	8.0
Sweating	5.0	5.2
Urogenital System	18.2	14.9
Urinary Tract Infection	6.1	3.5

[1] All patients on FASLODEX received injections, but only those anastrozole patients who were in the North American Study 2 received placebo injections.

Combination Therapy with Palbociclib

The safety of FASLODEX (500 mg) plus palbociclib (125 mg/day) versus FASLODEX plus placebo was evaluated in Study 4. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in Study 4.

No dose reduction was allowed for FASLODEX in Study 4. Dose reductions of palbociclib due to an adverse reaction of any grade occurred in 36% of patients receiving FASLODEX plus palbociclib.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving FASLODEX plus palbociclib, and in 6 of 172 (3%) patients receiving FASLODEX plus placebo. Adverse reactions leading to discontinuation for those patients receiving FASLODEX plus palbociclib included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions (≥10%) of any grade reported in patients in the FASLODEX plus palbociclib arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported serious adverse reactions in patients receiving FASLODEX plus palbociclib were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%).

Adverse reactions reported in patients who received FASLODEX plus palbociclib in Study 4 are listed in Table 3, and laboratory abnormalities are listed in Table 4.

Table 3: Adverse Reactions in Study 4

Adverse Reaction	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Infections and infestations						
Infections[a]	47	3	1	31	3	0
Blood and lymphatic system disorders						
Febrile neutropenia	1	1	0	1	0	1
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	3	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Eye disorders						
Vision blurred	6	0	0	2	0	0
Lacrimation increased	6	0	0	1	0	0
Dry eye	4	0	0	2	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Nervous system disorders						
Headache	26	1	0	20	0	0
Dysgeusia	7	0	0	3	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	7	0	0	2	0	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[b]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Constipation	20	0	0	16	0	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[c]	N/A	N/A	6[d]	N/A	N/A
Rash[e]	17	1	0	6	0	0
Dry skin	6	0	0	1	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0
Asthenia	8	0	0	5	1	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.

[a] Most common infections (>1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, bronchitis, rhinitis, conjunctivitis, pneumonia, sinusitis, cystitis, oral herpes, respiratory tract infection.

[b] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

[c] Grade 1 events – 17%; Grade 2 events – 1%.

[d] Grade 1 events – 6%.

[e] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Table 4: Laboratory Abnormalities in Study 4

Laboratory Abnormality	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0

N=number of patients; WBC=white blood cells.

6.2 Postmarketing Experience

For FASLODEX 250 mg, other adverse reactions reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, leukopenia, and hypersensitivity reactions including angioedema and urticaria.

Vaginal bleeding has been reported infrequently (<1%), mainly in patients during the first 6 weeks after changing from existing hormonal therapy to treatment with FASLODEX. If bleeding persists, further evaluation should be considered.

Elevation of bilirubin, elevation of gamma GT, hepatitis, and liver failure have been reported infrequently (<1%).

7 DRUG INTERACTIONS

There are no known drug-drug interactions. Although, fulvestrant is metabolized by CYP 3A4 *in vitro*, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP 3A4 inhibitors or inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, FASLODEX can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of fulvestrant to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicity, including skeletal malformations and fetal loss, at daily doses that were 6% and 30% of the maximum recommended human dose based on mg/m^2, respectively *[see Data]*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Administration of fulvestrant to rats prior to and up to implantation caused embryonic loss at daily doses that were 0.6% of the daily maximum recommended human dose based on mg/m^2. When fulvestrant was administered to pregnant rats during the period of organogenesis, intramuscular doses ≥0.1 mg/kg/day (6% of the human recommended dose based on mg/m^2) caused effects on embryo-fetal development consistent with its antiestrogenic activity. Fulvestrant caused an increased incidence of fetal abnormalities in rats (tarsal flexure of the hind paw at 2 mg/kg/day; equivalent to the human dose based on mg/m^2) and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥0.1 mg/kg/day. Fulvestrant administered at 2 mg/kg/day caused fetal loss.

When administered to pregnant rabbits during the period of organogenesis, fulvestrant caused pregnancy loss at an intramuscular dose of 1 mg/kg/day (equivalent to the human dose based on mg/m^2). Further, at 0.25 mg/kg/day (30% the human dose based on mg/m^2), fulvestrant caused increases in placental weight and post-implantation loss in rabbits. Fulvestrant was associated with an increased incidence of fetal variations in rabbits (backwards displacement of the pelvic girdle, and 27 pre-sacral vertebrae at 0.25 mg/kg/day; 30% the human dose based on mg/m^2) when administered during the period of organogenesis.

8.2 Lactation

Risk Summary

There is no information regarding the presence of fulvestrant in human milk, nor of its effects on milk production or breast-fed infant. Fulvestrant can be detected in rat milk *[see Data]*. Because of the potential for serious adverse reactions in breast-fed infants from FASLODEX, advise a lactating woman not to breast-feed during treatment with FASLODEX and for one year after the final dose.

Data

Levels of fulvestrant were approximately 12-fold higher in milk than in plasma after exposure of lactating rats to a dose of 2 mg/kg. Drug exposure in rodent pups from fulvestrant-treated lactating dams was estimated as 10% of the administered dose. In a study in rats of fulvestrant at 10 mg/kg given twice or 15 mg/kg given once (less than the recommended human dose based on mg/m^2) during lactation, offspring survival was slightly reduced.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating FASLODEX.

Contraception

Females

FASLODEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for one year after the last dose.

Infertility

Based on animal studies, FASLODEX may impair fertility in females and males of reproductive potential. The effects of fulvestrant on fertility were reversible in female rats *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. A multi-center, single-arm, open-label, study of fulvestrant was conducted in 30 girls with McCune-Albright Syndrome (MAS) associated with progressive precocious puberty (PPP). The median age at informed consent was 6 years old (range: 1 to 8).

The first 10 patients initially received fulvestrant 2 mg/kg. Based on PK data from the first 6 patients, all 10 patients receiving 2 mg/kg were escalated to a dose of 4 mg/kg and all other patients received 4 mg/kg from study entry.

Baseline measurements for vaginal bleeding days, bone age, growth velocity, and Tanner staging for at least 6 months prior to study entry were provided retrospectively by the parent, guardian or local consultant. All measurements during the study period were collected prospectively. Patients' baseline characteristics included the following: a mean ± SD chronological age of 5.9 ± 1.8 years; a mean rate of bone age advancement (change in bone age in years divided by change in chronological age in years) of 2.0 ± 1.03; and a mean growth velocity z-score of 2.4 ± 3.26.

Twenty-nine of 30 patients completed the 12-month study period. The following results were observed: 35% (95% CI: 16%, 57%) of the 23 patients with baseline vaginal bleeding experienced a complete cessation of vaginal bleeding on-treatment (month 0 to 12); a reduction in the rate of bone age advancement during the 12-month study period compared to baseline (mean change = -0.9 [95% CI: -1.4, -0.4]); and a reduction in mean growth velocity Z-score on-treatment compared to baseline (mean change = -1.1 [95% CI: -2.7, 0.4]). There were no clinically meaningful changes in median Tanner stage (breast or pubic), mean uterine volume, or mean ovarian volume, or predicted adult height (PAH) on-treatment compared to baseline. The effect of FASLODEX on bone mineral density in children has not been studied and is not known.

Eight patients (27%) experienced adverse reactions that were considered possibly related to FASLODEX. These included injection site reactions (inflammation, pain, hematoma, pruritus, rash), abdominal pain, contusion, tachycardia, hot flush, extremity pain, and vomiting. Nine (30.0%) patients reported an SAE, none of which were considered related to FASLODEX. No patients discontinued study treatment due to an AE and no patients died.

Pharmacokinetics

The pharmacokinetics of fulvestrant was characterized using a population pharmacokinetic analysis with sparse samples per patient obtained from 30 female pediatric patients aged 1 to 8 years with PPP

associated with MAS. Pharmacokinetic data from 294 postmenopausal women with breast cancer who received 125 or 250 mg monthly dosing regimen were also included in the analysis.

In these pediatric patients receiving 4 mg/kg monthly intramuscular dose of fulvestrant, the geometric mean (SD) CL/F was 444 (165) mL/min which was 32% lower than adults. The geometric mean (SD) steady state trough concentration ($C_{min,ss}$) and AUC_{ss} was 4.19 (0.87) ng/mL and 3680 (1020) ng*hr/mL, respectively.

8.5 Geriatric Use

For FASLODEX 250 mg, when tumor response was considered by age, objective responses were seen in 22% and 24% of patients under 65 years of age and in 11% and 16% of patients 65 years of age and older, who were treated with FASLODEX in Study 2 and Study 3, respectively.

8.6 Hepatic Impairment

FASLODEX is metabolized primarily in the liver.

The pharmacokinetics of fulvestrant were evaluated after a single dose of 100 mg in subjects with mild and moderate hepatic impairment and normal hepatic function (n = 7 subjects/group), using a shorter-acting intramuscular injection formulation. Subjects with mild hepatic impairment (Child-Pugh class A) had comparable mean AUC and clearance values to those with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh class B), the average AUC of fulvestrant increased by 70% compared to patients with normal hepatic function. AUC was positively correlated with total bilirubin concentration (p = 0.012). FASLODEX has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

A dose of FASLODEX 250 mg is recommended in patients with moderate hepatic impairment (Child-Pugh class B) *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

8.7 Renal Impairment

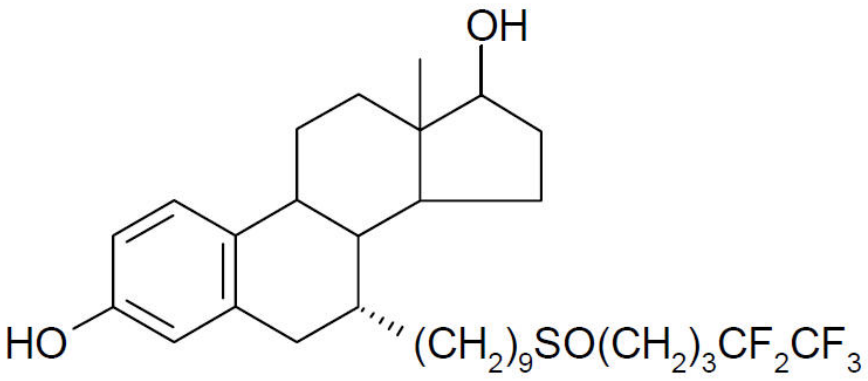
Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine.

10 OVERDOSAGE

Animal studies have shown no effects other than those related directly or indirectly to antiestrogen activity with intramuscular doses of fulvestrant higher than the recommended human dose. There is no clinical experience with overdosage in humans. No adverse reactions were seen in healthy male and female volunteers who received intravenous fulvestrant, which resulted in peak plasma concentrations at the end of the infusion, that were approximately 10 to 15 times those seen after intramuscular injection.

11 DESCRIPTION

FASLODEX® (fulvestrant) injection for intramuscular administration is an estrogen receptor antagonist. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol. The molecular formula is $C_{32}H_{47}F_5O_3S$ and its structural formula is:



Fulvestrant is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Each injection contains as inactive ingredients: 10% w/v Alcohol, USP, 10% w/v Benzyl Alcohol, NF, and 15% w/v Benzyl Benzoate, USP, as co-solvents, and made up to 100% w/v with Castor Oil, USP as a co-solvent and release rate modifier.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Many breast cancers have estrogen receptors (ER) and the growth of these tumors can be stimulated by estrogen. Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human breast cancer cells.

In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In *in vivo* tumor studies, fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts.

Fulvestrant showed no agonist-type effects in *in vivo* uterotropic assays in immature or ovariectomized mice and rats. In *in vivo* studies in immature rats and ovariectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects.

12.2 Pharmacodynamics

In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation.

12.3 Pharmacokinetics

Absorption:

The single dose and multiple dose PK parameters for the 500 mg dosing regimen with an additional dose (AD) at Day 15 are reported in Table 5. The additional dose of FASLODEX given two weeks after the initial dose allows for steady state concentrations to be reached within the first month of dosing.

Table 5: Summary of Fulvestrant Pharmacokinetic Parameters [gMean (CV%)] in Postmenopausal Advanced Breast Cancer Patients after Intramuscular Administration 500 mg + AD Dosing Regimen

		C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (ng.hr/mL)
500 mg + AD[1]	Single dose	25.1 (35.3)	16.3 (25.9)	11400 (33.4)
	Multiple dose steady state[2]	28.0 (27.9)	12.2 (21.7)	13100 (23.4)

[1] Additional 500 mg dose given on Day 15

[2] Month 3

Distribution:

The apparent volume of distribution at steady state is approximately 3 to 5 L/kg. This suggests that distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins; VLDL, LDL and HDL lipoprotein fractions appear to be the major binding components. The role of sex hormone-binding globulin, if any, could not be determined.

Metabolism:

Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of ^{14}C-labeled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate at the 2, 3 and 17 positions of the steroid nucleus, and oxidation of the side chain sulphoxide. Identified metabolites are either less active or exhibit similar activity to fulvestrant in antiestrogen models.

Studies using human liver preparations and recombinant human enzymes indicate that cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of P-450 and non-P-450 routes *in vivo* is unknown.

Excretion:

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%). After an intramuscular injection of 250 mg, the clearance (Mean ± SD) was 690 ± 226 mL/min with an apparent half-life about 40 days.

Special Populations:

Geriatric:

In patients with breast cancer, there was no difference in fulvestrant pharmacokinetic profile related to age (range 33 to 89 years).

Gender:

Following administration of a single intravenous dose, there were no pharmacokinetic differences between men and women or between premenopausal and postmenopausal women. Similarly, there were no differences between men and postmenopausal women after intramuscular administration.

Race:

In the advanced breast cancer treatment trials, the potential for pharmacokinetic differences due to race have been evaluated in 294 women including 87.4% Caucasian, 7.8% Black, and 4.4% Hispanic. No differences in fulvestrant plasma pharmacokinetics were observed among these groups. In a separate trial, pharmacokinetic data from postmenopausal ethnic Japanese women were similar to those obtained in non-Japanese patients.

Drug-Drug Interactions:

There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP 3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers *[see Drug Interactions (7)]*. Data from a clinical trial in patients with breast cancer showed that there was no clinically relevant drug interaction between fulvestrant and palbociclib when the two drugs were co-administered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenesis studies were conducted in rats and mice. Positive findings were observed in both species. Rats were treated at intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days.

These doses correspond to 0.9-, 1.5-, and 3-fold (in females) and 0.8-, 0.8-, and 2-fold (in males) the systemic exposure [$AUC_{0\text{-}30\ days}$] achieved in women receiving the recommended dose of 500 mg/month. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Mice were treated at oral doses of 0, 20, 150 and 500 mg/kg/day. These doses correspond to 0, 0.8, 8.4 and 18-fold (in females) and 0.8-, 7.1- and 11.9- fold (in males), the systemic exposure ($AUC_{0\text{-}30\ days}$) achieved in women receiving the recommended dose of 500 mg/month. There was an increased incidence of sex cord stromal tumors (both benign and malignant) in the ovary of mice at doses of 150 and 500 mg/kg/day. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Fulvestrant was not mutagenic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of Salmonella typhimurium and Escherichia coli, *in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells and *in vivo* micronucleus test in rat).

In female rats, fulvestrant administered at doses ≥0.01 mg/kg/day (0.6% the human recommended dose based on body surface area [BSA in mg/m^2]), for 2 weeks prior to and for 1 week following mating, caused a reduction in fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.001 mg/kg/day (0.06% the human dose based on BSA in mg/m^2). Restoration of female fertility to values similar to controls was evident following a 29-day withdrawal period after dosing at 2 mg/kg/day (equivalent to the human dose based on BSA in mg/m^2). The effects of fulvestrant on the fertility of female rats appear to be consistent with its antiestrogenic activity. The potential effects of fulvestrant on the fertility of male animals were not studied but, in a 6-month toxicology study, male rats treated with intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days fulvestrant showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing. These fulvestrant doses correspond to 1.3-, 1.2- and 3.5-fold the systemic exposure [$AUC_{0\text{-}30\ days}$] achieved in women receiving the recommended dose of 500 mg/month.

14 CLINICAL STUDIES

The efficacy of FASLODEX 500 mg versus FASLODEX 250 mg was compared in Study 1. The efficacy of FASLODEX 250 mg was compared to anastrozole in Studies 2 and 3. The efficacy of FASLODEX 500 mg in combination with palbociclib 125 mg was compared to FASLODEX 500 mg plus placebo in Study 4.

Monotherapy

Comparison of FASLODEX 500 mg and FASLODEX 250 mg (Study 1)

A Phase 3 randomized, double-blind, controlled clinical trial (Study 1) was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. This trial compared the efficacy and safety of FASLODEX 500 mg (n=362) with FASLODEX 250 mg (n=374).

FASLODEX 500 mg was administered as two 5 mL injections each containing FASLODEX 250 mg/5mL, one in each buttock, on Days 1, 15, 29 and every 28 (+/- 3) days thereafter. FASLODEX 250 mg was administered as two 5 mL injections (one containing FASLODEX 250 mg/5mL injection plus one placebo injection), one in each buttock, on Days 1, 15 (2 placebo injections only), 29 and every 28 (+/- 3) days thereafter.

The median age of study participants was 61. All patients had ER+ advanced breast cancer. Approximately 30% of subjects had no measurable disease. Approximately 55% of patients had visceral disease.

Results of Study 1 are summarized in Table 6. The efficacy of FASLODEX 500 mg was compared to that of FASLODEX 250 mg. Figure 4 shows a Kaplan-Meier plot of the Progression Free Survival (PFS) data after a minimum follow-up duration of 18 months demonstrating statistically significant superiority of FASLODEX 500 mg *vs.* FASLODEX 250 mg. In the initial Overall Survival (OS) analysis after a minimum follow-up duration of 18 months, there was no statistically significant difference in OS between the two treatment groups. After a minimum follow-up duration of 50 months, an updated OS analysis was performed. Figure 5 shows a Kaplan-Meier plot of the updated OS data.

Table 6: Efficacy Results Study 1: Intent-To-Treat (ITT) Population

Endpoint	**Fulvestrant 500 mg (N=362)**	**Fulvestrant 250 mg (N=374)**
PFS[1] Median (months)	6.5	5.4
Hazard Ratio[2] (95% CI[3])	0.80 (0.68-0.94)	
p-value	0.006	
OS[4] **Updated Analysis**[5] (% patients who died)	261 (72.1%)	293 (78.3%)
Median OS (months)	26.4	22.3
Hazard Ratio[2] (95% CI[3])[6]	0.81 (0.69-0.96)	
ORR[7] (95% CI[3])	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) 38/261)

1 PFS (Progression Free Survival) = the time between randomization and the earliest of progression or death from any cause. Minimum follow-up duration of 18 months.

2 Hazard Ratio <1 favors FASLODEX 500 mg.

3 CI=Confidence Interval

4 OS=Overall Survival

5. **Minimum follow up duration of 50 months.**

6 Not statistically significant as no adjustments were made for multiplicity.

7 ORR (Objective Response Rate), as defined as number (%) of patients with complete response or partial response, was analyzed in the evaluable patients with measureable disease at baseline (fulvestrant 500 mg N=240; fulvestrant 250 mg N=261). Minimum follow-up duration of 18 months.

Figure 4 Kaplan-Meier PFS: Study 1 ITT Population

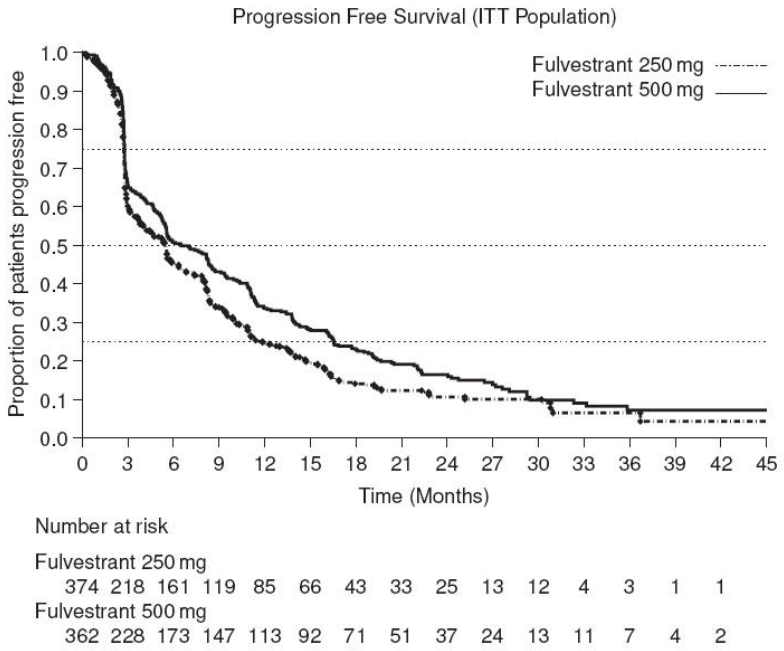
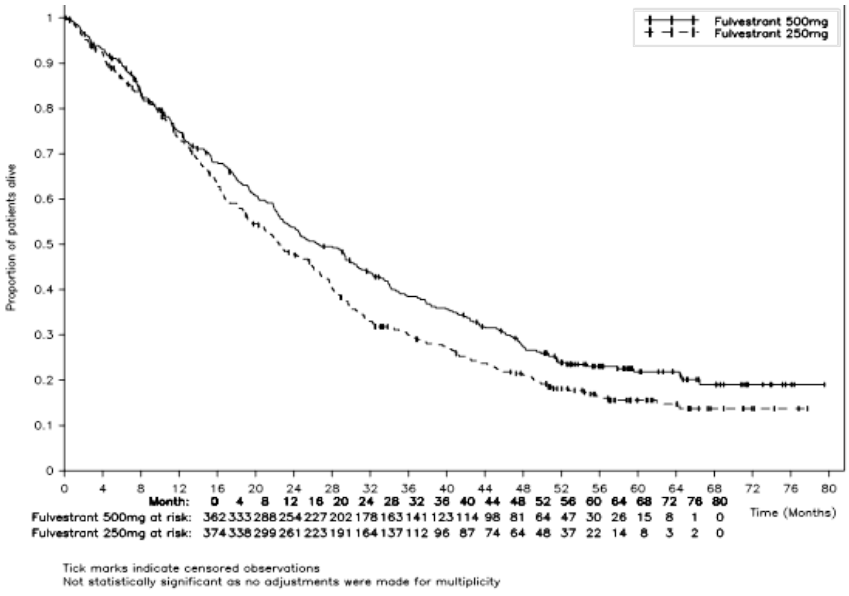


Figure 5 Kaplan-Meier OS (Minimum Follow-up Duration of 50 Months): Study 1 ITT Population



Comparison of FASLODEX 250 mg and Anastrozole 1 mg in Combined Data (Studies 2 and 3)

Efficacy of FASLODEX was established by comparison to the selective aromatase inhibitor anastrozole in two randomized, controlled clinical trials (one conducted in North America, Study 2; the other predominantly in Europe, Study 3) in postmenopausal women with locally advanced or metastatic breast

cancer. All patients had progressed after previous therapy with an antiestrogen or progestin for breast cancer in the adjuvant or advanced disease setting.

The median age of study participants was 64. 81.6% of patients had ER+ and/or PgR+ tumors. Patients with ER- /PgR- or unknown tumors were required to have demonstrated a prior response to endocrine therapy. Sites of metastases occurred as follows: visceral only 18.2%; viscera – liver involvement 23.0%; lung involvement 28.1%; bone only 19.7%; soft tissue only 5.2%; skin and soft tissue 18.7%.

In both trials, eligible patients with measurable and/or evaluable disease were randomized to receive either FASLODEX 250 mg intramuscularly once a month (28 days $\pm$ 3 days) or anastrozole 1 mg orally once a day. All patients were assessed monthly for the first three months and every three months thereafter. Study 2 was a double-blind, randomized trial in 400 postmenopausal women. Study 3 was an open-label, randomized trial conducted in 451 postmenopausal women. Patients on the FASLODEX arm of Study 2 received two separate injections (2 X 2.5 mL), whereas FASLODEX patients received a single injection (1 X 5 mL) in Study 3. In both trials, patients were initially randomized to a 125 mg per month dose as well, but interim analysis showed a very low response rate, and low dose groups were dropped.

Results of the trials, after a minimum follow-up duration of 14.6 months, are summarized in Table 7. The effectiveness of FASLODEX 250 mg was determined by comparing Objective Response Rate (ORR) and Time to Progression (TTP) results to anastrozole 1 mg, the active control. The two studies ruled out (by one-sided 97.7% confidence limit) inferiority of FASLODEX to anastrozole of 6.3% and 1.4% in terms of ORR. There was no statistically significant difference in overall survival (OS) between the two treatment groups after a follow-up duration of 28.2 months in Study 2 and 24.4 months in Study 3.

Table 7: Efficacy Results

	Study 2 (Double-Blind)		**Study 3 (Open-Label)**	
	FASLODEX	**Anastrozole**	**FASLODEX**	**Anastrozole**
Endpoint	**250 mg (n=206)**	**1 mg (n=194)**	**250 mg (n=222)**	**1 mg (n=229)**
Objective Tumor Response Number (%) of subjects with CR[1] + PR[2]	35 (17.0)	33 (17.0)	45 (20.3)	34 (14.9)
% Difference in Tumor Response Rate (FAS[3]-ANA[4]) 2–sided 95.4% CI[5]	0.0 (-6.3, 8.9)		5.4 (-1.4, 14.8)	
Time to Progression (TTP) Median TTP (days)	165	103	166	156
Hazard Ratio [6] 2-sided 95.4% CI	0.9 (0.7, 1.1)		1.0 (0.8, 1.2)	
Stable Disease for ≥24 weeks (%)	26.7	19.1	24.3	30.1
Overall Survival (OS)				
Died n (%)	152 (73.8%)	149 (76.8%)	167 (75.2%)	173 (75.5%)
Median Survival (days)	844	913	803	736
Hazard Ratio[6]	0.98		0.97	

	Study 2 (Double-Blind)		Study 3 (Open-Label)	
	FASLODEX	**Anastrozole**	**FASLODEX**	**Anastrozole**
Endpoint	**250 mg (n=206)**	**1 mg (n=194)**	**250 mg (n=222)**	**1 mg (n=229)**
(2-sided 95% CI)	(0.78, 1.24)		(0.78, 1.21)	

[1] CR = Complete Response
[2] PR = Partial Response
[3] FAS = FASLODEX
[4] ANA = anastrozole
[5] CI = Confidence Interval
[6] Hazard Ratio <1 favors FASLODEX

Combination Therapy

FASLODEX 500 mg in Combination with Palbociclib 125 mg (Study 4)

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

Study 4 was an international, randomized, double-blind, parallel group, multicenter study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose diseased progressed on or after prior endocrine therapy.

A total of 521 pre/postmenopausal women were randomized 2:1 to FASLODEX plus palbociclib or FASLODEX plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Fulvestrant 500 mg was administered as two 5 mL injections each containing fulvestrant 250 mg/5mL, one in each buttock, on Days 1, 15, 29 and every 28 (+/- 3) days thereafter. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of Study 4.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients in each treatment arm were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS from Study 4 are summarized in Table 8 and Figure 6. Consistent results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy and menopausal status. Confirmed overall response rate in patients with measurable disease as

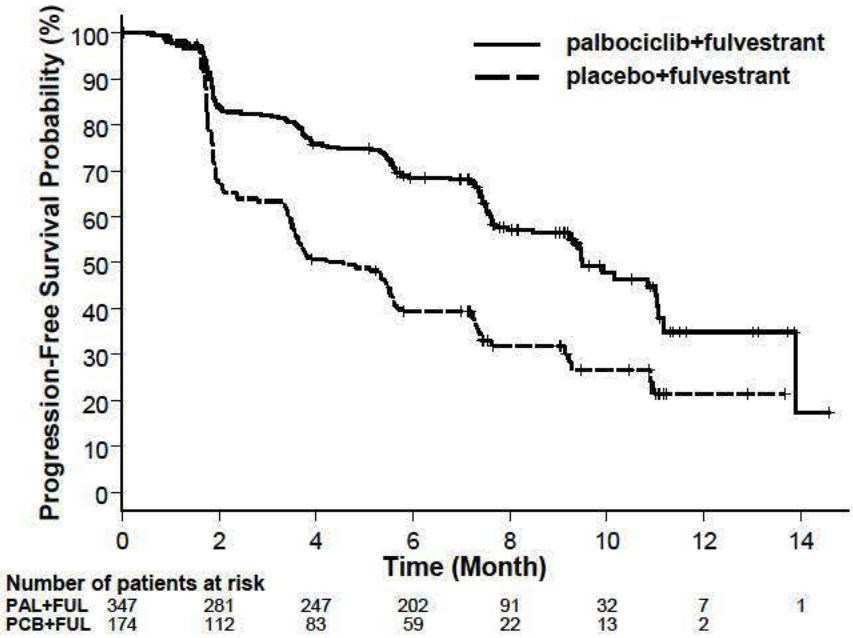
assessed by the investigator was 24.6% in the FASLODEX plus palbociclib and was 10.9% in the FASLODEX plus placebo arm. Duration of response was 9.3 months in the FASLODEX plus palbociclib arm compared with 7.6 months in the FASLODEX plus placebo arm. At the time of final analysis of PFS, OS data were not mature with 29% of events.

Table 8: Efficacy Results – Study 4 (Investigator Assessment, ITT Population)

	FASLODEX plus palbociclib (N=347)	**FASLODEX plus placebo (N=174)**
Progression-Free Survival		
Number of PFS Events (%)	145 (41.8%)	114 (65.5%)
Hazard Ratio (95% CI) and p-value	0.461 (0.360-0.591) p <0.0001	
Median PFS (months) (95% CI)	9.5 (9.2-11.0)	4.6 (3.5-5.6)

N=number of patients.
CI=confidence interval.

Figure 6 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, ITT Population) — Study 4



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

FASLODEX is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and fitted with a tamper evident closure.

NDC 0310–0720–10

The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Storage:

REFRIGERATE, 2°-8°C (36°-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Monotherapy

Risk of Bleeding:

- Because FASLODEX is administered intramuscularly, it should be used with caution in patients with bleeding disorders, decreased platelet count, or in patients receiving anticoagulants (for example, warfarin) *[see Warnings and Precautions (5.1)].*

Embryo-Fetal Toxicity:

- Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with FASLODEX and for one year after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1), (8.3)].*

Lactation:

- Advise women not to breast-feed during treatment with FASLODEX and for one year after the last dose *[see Use in Specific Populations (8.2)]*.

Combination Therapy with Palbociclib

See palbociclib full prescribing information for Patient Counseling Information.

PATIENT INFORMATION

FASLODEX® (faz-lo-dex)

(fulvestrant)

Injection

What is FASLODEX?

FASLODEX is a prescription medicine used to treat:

- hormone receptor (HR)-positive breast cancer in women who have gone through menopause whose disease has spread after treatment with an antiestrogen medicine, OR
- HR-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer whose disease has spread to other parts of the body (metastatic) in combination with palbociclib in women with disease progression after hormonal therapy

When FASLODEX is used in combination with palbociclib, please also see the palbociclib Patient Information.

It is not known if FASLODEX is safe and effective in children.

It is not known if FASLODEX is safe and effective in people with severe liver problems.

Who should not receive FASLODEX?

Do not receive FASLODEX if you have had an allergic reaction to any of the ingredients in FASLODEX. See the end of this leaflet for a list of the ingredients in FASLODEX.

Symptoms of an allergic reaction to FASLODEX may include:

- itching
- swelling of your face, lips, tongue or throat
- trouble breathing

What should I tell my healthcare provider before receiving FASLODEX?

Before receiving FASLODEX, tell your healthcare provider about all of your medical conditions, including if you:

- have a low level of platelets in your blood or bleed easily.
- have liver problems.
- are pregnant or plan to become pregnant. FASLODEX can harm your unborn baby.
    - Females who are able to become pregnant should use effective birth control during treatment with FASLODEX and for one year after the last dose of FASLODEX.
    - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with FASLODEX.
- are breast-feeding or plan to breast-feed. It is not known if FASLODEX passes into your breast milk. Do not breast-feed during your treatment with FASLODEX and for one year after the last dose of FASLODEX. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over the counter medicines, vitamins, and herbal supplements. FASLODEX may affect the way other medicines work, and other medicines may affect how FASLODEX works.

Especially tell your healthcare provider if you take a blood thinner medicine.

How will I receive FASLODEX?

- Your healthcare provider will give you FASLODEX by injection into the muscle of your buttock.
- Your healthcare provider may change your dose of FASLODEX if needed.

What are the possible side effects of FASLODEX?

Common side effects of FASLODEX include:

- injection site pain
- nausea
- muscle, joint, and bone pain
- headache
- tiredness
- hot flashes
- vomiting
- loss of appetite
- weakness
- cough
- shortness of breath
- constipation
- increased liver enzymes

FASLODEX may cause fertility problems in males and females. Talk to your healthcare provider if you plan to become pregnant.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects with FASLODEX. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of FASLODEX

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use FASLODEX for a condition for which it was not prescribed. Do not give FASLODEX to other people, even if they have the same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about FASLODEX that is written for health professionals.

What are the ingredients in FASLODEX?

Active ingredient: fulvestrant.

Inactive ingredients: alcohol, benzyl alcohol, benzyl benzoate, and castor oil.

Distributed by:

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Manufactured for:

AstraZeneca UK Limited
Macclesfield, Cheshire, England

By: Vetter Pharma-Fertigung GMBH & Co. KG
Ravensburg, Germany

For more information, go to www.FASLODEX.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: March 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

OFFICER/EMPLOYEE LIST

Officer / Employee List
Application: sNDA 021344/026

The Following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Amiri-Kordestani, Laleh
Bloomquist, Erik
Dinatale, Miriam
Fedenko, Kathryn
Fourie-Zirkelbach, Jeanne
Ibrahim, Amna
Kacuba, Alice
Kim, Geoffrey
Jenney, Susan
Liu, Qi
Mills, Sharon
Palmby, Todd
Pierce, William
Ringgold, Kimberly
Senior, Nicholas
Song, Pengfei
Tang, Shenghui
Tilley, Amy
Walker, Amanda
Walker, Morgan
Wedam, Suparna
Yu, Jingyu (Jerry)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

OFFICE DIRECTOR MEMO

Division Director Summary Review for Regulatory Action

Date	February 19, 2016
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	021344/S026
Applicant	AstraZeneca Pharmaceuticals LP
Date of Submission	November 17, 2015
PDUFA Goal Date	November 17, 2016
Proprietary Name / **Non-Proprietary Name**	FASLODEX/fulvestrant
Dosage Form(s) / Strength(s)	Injection, 500 mg
Applicant Proposed Indication(s)/Population(s)	In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative [redacted] (b) (4)
Action/Recommended Action for sNDA:	*Approval*
Approved/Recommended Indication/Population(s) (if applicable)	In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic cancer with disease progression following endocrine therapy.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Suparna Wedam; Amanda Walker
Statistical Review	Erik Bloomquist; Shenghui Tang

CDTL Review	Laleh Amiri-Kordestani

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

I concur with the Benefit-Risk Assessment that was made by the clinical and statistical teams. Based on the results of Study 1023 (PALOMA-3), a favorable benefit-risk profile has been demonstrated for patients with HR-positive, HER2-negativeadvanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy. The regulatory action for this supplement is approval. As summarized by the clinical review team:

*"*The benefit-risk assessment in this sNDA is based on the phase 3 Study 1023 (PALOMA-3). Study 1023 was a randomized, double-blind, placebo-controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed on prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed PFS. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; p<0.000001). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months n the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. Overall survival (OS) results are immature at this time.

Overall, palbociclib plus fulvestrant was generally tolerable with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care. Neutropenia was the most common adverse event occurring in >80% of patients. It is reassuring, however, that there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib plus fulvestrant include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus fulvestrant compared to patients receiving placebo plus fulvestrant, suggesting that palbociclib may increase the risk of pulmonary emboli. . With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation due to adverse reactions were generally low.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "FASLODEX is an estrogen receptor antagonist indicated in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast

cancer whose disease progressed after endocrine therapy.
The Table below is from the combined clinical and statistical review. I concur with the findings and analysis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	In 2016, it is estimated that breast cancer will be diagnosed in 246,660 women in the United States and that approximately 40,000 women will die of their disease. MBC, where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%.	Breast cancer is a serious and life-threatening condition.
Current Treatment Options	The treatment of MBC is palliative in nature with a goal to prolong survival and improve quality of life by reducing cancer-related symptoms. Endocrine therapy options for postmenopausal women with HR-positive MBC include aromatase inhibitors (anastrozole, letrozole and exemestane), fulvestrant or tamoxifen. Pre- and post-menopausal women may also receive chemotherapy as second or later lines of treatment, once they have had tumor progression on endocrine therapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.	There are unmet medical needs to improve the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
Benefit	The clinical data from a randomized, double-blind, placebo controlled Phase 3 Trial (Study 1023, A5481023, PALOMA-3) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy presented in this sNDA demonstrates an improvement in PFS for palbociclib plus fulvestrant compared to placebo plus fulvestrant. The median PFS in the palbociclib plus fulvestrant arm was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR =0.46; 95% CI: 0.36, 0.59; p<0.000001). OS results were immature at the time of analysis with only 29% of the planned 198 events. Overall response rate	The PFS benefit derived from palbociclib in combination with FASLODEX is statistically significant and clinically meaningful. It is unclear if there will be an OS benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(ORR) was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline. Duration of response (DOR) was 9.3 months in the palbociclib plus fulvestrant arm and 7.6 months in the placebo plus fulvestrant arm.	
Risk	Neutropenia was reported in >70% of patients taking palbociclib and was the most common reason for temporary discontinuation and/or dose reduction; however, there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation for adverse reactions were generally low. No new safety concerns have been identified based on the cumulative safety data submitted in this sNDA.	The safety profile of palbociclib plus fulvestrant for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care.
Risk Management	• There is no proposal for a formal Risk management Plan.	

2. Background

From the clinical and statistical review:
This is a supplemental New Drug Application (sNDA) for FASLODEX in patients with advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

The Applicant proposed the following supplemental indication for the FASLODEX label:
"FASLODEX is an estrogen receptor antagonist indicated in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

Division Director's Comment:
The applicant has submitted this sNDA for the reverse parallel labeling extension for Faslodex on the basis of the PALOMA-3 trial (Study 1023) in order to ensure consistency across labeling for fulvestrant and palbociclib. The applicant obtained a collaborative agreement with the manufacturer of palbociclib to cross reference their application to sNDA 207103 S2.

The FDA review of the PALOMA-3 trial is described in great detail under sNDA 20710. The major review issue for this application is whether labeling for fulvestrant was warranted as the study was not designed to isolate the effect of fulvestrant. Conceptually, it is feasible that the efficacy seen with the combination of fulvestrant and palbociclib was driven entirely by palbociclib and that the addition of fulvestrant was not needed. This lack of the isolation of effect is the key reason why numerous "backbone" agents in oncology are not "cross-labeled" when a novel drug is approved on the basis of a trial with an "add-on" design.

*For this application, the review team carefully assessed data available outside this clinical trial that could provide information to support the omission of a palbociclib monotherapy arm in Study 1023). As per the clinical/statistical review "*palbociclib has limited single agent activity (2,3). No responses [partial response (PR) or complete response (CR) as per RECIST criteria] were seen in a phase 1 dose-escalation study conducted with palbociclib in patients with retinoblastoma protein (Rb)-positive advanced solid tumors. A subsequent phase 2 study using single agent palbociclib in patients with Rb-positive advanced breast cancer resulted in an ORR of 5% in all patients (n=37) and 6% in patients with HR-positive disease (n=33) (4). Yet, a clinically meaningful benefit has been demonstrated when palbociclib is given in combination with endocrine therapies such as letrozole or fulvestrant (5,6). Ideally, a factorial study design would allow us to isolate the effect of each of the agents (palbociclib and fulvestrant), but conducting such a trial would involve administering a treatment known to be ineffective as monotherapy. Instead, evidence for the efficacy and safety of the combination of palbociclib plus fulvestrant was established with an add-on design in Study 1023. An improvement in clinical benefit was seen in Study 1023 with the addition of palbociclib to fulvestrant compared to fulvestrant therapy alone. Therefore, although the effect of fulvestrant cannot be isolated from the comparison of these two treatment arms, reverse parallel labeling is warranted for fulvestrant given the clinically meaningful and statistically

significant improvement in median PFS in the combination arm." *I concur with the review team. The lack of meaningful anti-tumor activity observed with palbociclib monotherapy justified the omission of the palbociclib monotherapy arm in Study 1023. This is consistent with current FDA advice presented in the* Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination, *which states: "*If findings from in vivo or in vitro models and/or phase 2 trials adequately demonstrate the contribution of each new investigational drug to the combination, phase 3 trials comparing the combination to SOC or placebo generally will be sufficient to establish effectiveness." *Study 1023 has demonstrated the improved efficacy of the combination of fulvestrant and palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in women with disease progression following endocrine therapy. The safety profile of the combination is acceptable.*

3. Labeling

Agreement has been reached on the physician labeling. The final indication is in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic cancer with disease progression following endocrine therapy.

The changes to the efficacy (14) and safety (5, 6) sections of the package insert are discussed in the review of sNDA 207103 S2.

4. Postmarketing

There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies. There are no postmarketing commitments or requirements.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
03/01/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	021344/26
Priority or Standard	Standard
Submit Date(s)	November 17, 2015
Received Date(s)	November 17, 2015
PDUFA Goal Date	November 17, 2016
Division/Office	DOP1/OHOP
Clinical Reviewer Name(s)	Suparna Wedam, MD/Amanda Walker, MD
Statistical Reviewer Name	Erik Bloomquist, PhD
Statistical Team Leader	Shenghui Tang, PhD
CDTL Name	Laleh Amiri-Kordestani, MD
Review Completion Date	February 19, 2016
Established Name	Fulvestrant
(Proposed) Trade Name	FASLODEX®
Applicant	AstraZeneca Pharmaceuticals LP
Formulation(s)	Intramuscular injections
Dosing Regimen	500mg on days 1, 15, 29 and once monthly thereafter intramuscularly
Applicant Proposed Indication(s)/Population(s)	In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s)	In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic cancer with disease progression following endocrine therapy.

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Glossary

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

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

1 Executive Summary

1.1. Product Introduction

This is a supplemental New Drug Application (sNDA) for FASLODEX in patients with advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

The Applicant proposed the following supplemental indication for the FASLODEX label:

"FASLODEX is an estrogen receptor antagonist indicated in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical review team recommends regular approval of FASLODEX (fulvestrant) for the following indication:

> *"FASLODEX is an estrogen receptor antagonist indicated in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer whose disease progressed after endocrine therapy."*

The basis for this recommendation is a favorable benefit-risk profile for combination palbociclib and fulvestrant therapy in women with HR-positive, HER2-negative advanced or metastatic breast cancer that has progressed on prior endocrine therapy. In the pivotal randomized, double-blind, placebo- controlled Phase 3 study, Study 1023 (A5481023, PALOMA-3) a clinically meaningful and statistically significant improvement in median progression free survival (PFS) was observed favoring the palbociclib plus fulvestrant treatment arm. Results of a blinded independent central review (BICR) audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; p<0.000001). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). In addition, overall response rate (ORR), per investigator-assessment was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline.

Fulvestrant has known single agent activity and has been approved as monotherapy in the US

since 2002 for the treatment of postmenopausal women with HR-positive metastatic breast cancer whose disease has progressed following antiestrogen therapy (1). Conversely, palbociclib has limited single agent activity (2,3). No responses [partial response (PR) or complete response (CR) as per RECIST criteria] were seen in a phase 1 dose-escalation study conducted with palbociclib in patients with retinoblastoma protein (Rb)-positive advanced solid tumors. A subsequent phase 2 study using single agent palbociclib in patients with Rb-positive advanced breast cancer resulted in an ORR of 5% in all patients (n=37) and 6% in patients with HR-positive disease (n=33) (4). Yet, a clinically meaningful benefit has been demonstrated when palbociclib is given in combination with endocrine therapies such as letrozole or fulvestrant (5,6). Ideally, a factorial study design would allow us to isolate the effect of each of the agents (palbociclib and fulvestrant), but conducting such a trial would involve administering a treatment known to be ineffective as monotherapy. Instead, evidence for the efficacy and safety of the combination of palbociclib plus fulvestrant was established with an add-on design in Study 1023. An improvement in clinical benefit was seen in Study 1023 with the addition of palbociclib to fulvestrant compared to fulvestrant therapy alone. Therefore, although the effect of fulvestrant cannot be isolated from the comparison of these two treatment arms, reverse parallel labeling is warranted for fulvestrant given the clinically meaningful and statistically significant improvement in median PFS in the combination arm.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer among US women (excluding cancers of the skin), accounting for 29% of newly diagnosed cancers. In 2016, it is estimated that breast cancer will be diagnosed in 246,660 women in the United States and that approximately 40,000 women will die of their disease (7). Breast cancer can be categorized into different histopathologic subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 overexpression. HR-positive/HER2-negative breast cancer is the most common subset of breast cancer. Most patients are diagnosed at an early stage and treated with endocrine therapy with or without chemotherapy. About one-third of all HR-positive/HER2-negative patients, diagnosed initially with early stage disease, experience metastatic or recurrent disease (8, 9). Endocrine therapy is the preferred option at the time of disease recurrence. Not all patients respond to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). Further treatment options at the time of recurrence include subsequent endocrine therapy or chemotherapy. Metastatic breast cancer (MBC), where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20% (8). Therefore, there is an unmet medical need to improve the outcomes in patients with advanced or metastatic breast cancer.

The Applicant submitted a sNDA application for fulvestrant in combination with palbociclib with a proposed indication for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have received prior endocrine therapy. Fulvestrant is an estrogen receptor antagonist (1). Palbociclib is a reversible inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6 and thus acts to prevent cellular proliferation by blocking G1 to S phase transition of the cell cycle (10,11). Palbociclib was granted accelerated approval by the FDA on February 3, 2015 for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease (12).

The benefit-risk assessment in this sNDA is based on the phase 3 Study 1023 (PALOMA-3). Study 1023 was a randomized, double-blind, placebo-controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed on prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed PFS. The median PFS in the palbociclib plus fulvestrant arm at the time of the preplanned interim analysis was 9.2 months compared to 3.8 months in the placebo plus fulvestrant arm (HR=0.42; 95%CI: 0.32, 0.56; p<0.000001). The results were consistent at the time of the updated and final analysis with a median PFS of 9.5 months in the palbociclib plus fulvestrant arm compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. Overall survival (OS) results are immature at this time.

Overall, palbociclib plus fulvestrant was generally tolerable with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care. Neutropenia was the most common adverse event occurring in >80% of patients. It is reassuring, however, that there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib plus fulvestrant include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib plus fulvestrant compared to patients receiving placebo plus fulvestrant, suggesting that palbociclib may increase the risk of pulmonary emboli. . With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation due to adverse reactions were generally low.

In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "FASLODEX is an estrogen receptor antagonist indicated in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer whose disease progressed after endocrine therapy."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2016, it is estimated that breast cancer will be diagnosed in 246,660 women in the United States and that approximately 40,000 women will die of their disease. MBC, where the original cancer in the breast has spread to distant organs in the body, is the most advanced stage of breast cancer and is incurable with a 5 year survival of approximately 20%.	Breast cancer is a serious and life-threatening condition.
Current Treatment Options	• The treatment of MBC is palliative in nature with a goal to prolong survival and improve quality of life by reducing cancer-related symptoms. Endocrine therapy options for postmenopausal women with HR-positive MBC include aromatase inhibitors (anastrozole, letrozole and exemestane), fulvestrant or tamoxifen. Endocrine therapy options for premenopausal women with HR-positive MBC	There is an unmet medical need to improve the outcomes in patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that do not respond to first line therapy are similar to those for postmenopausal women; however, aromatase inhibitors or fulvestrant need to be administered in combination with ovarian suppression therapy. Pre- and post-menopausal women may also receive chemotherapy as second or later lines of treatment, once they have had tumor progression on endocrine therapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.	
Benefit	• The clinical data from a randomized, double-blind, placebo-controlled Phase 3 Trial (Study 1023, A5481023, PALOMA-3) in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy presented in this sNDA demonstrates an improvement in PFS for palbociclib plus fulvestrant compared to placebo plus fulvestrant. The median PFS in the palbociclib plus fulvestrant arm was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR =0.46; 95% CI: 0.36, 0.59; p<0.000001). OS results were immature at the time of analysis with only 29% of the planned 198 events. Overall response rate (ORR) was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline. Duration of response (DOR) was 9.3 months in the palbociclib plus fulvestrant arm and 7.6 months in the placebo plus fulvestrant arm.	The PFS benefit derived from palbociclib in combination with fulvestrant is statistically significant and clinically meaningful.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• Neutropenia was reported in >80% of patients taking palbociclib plus fulvestrant and was the most common reason for temporary discontinuation and/or dose reduction; however, there were very few cases of neutropenic fever and neutropenic sepsis. Additional common adverse reactions with palbociclib plus fulvestrant include leukopenia (53%), infections (47%), fatigue (41%), nausea (34%), anemia (30%), stomatitis (28%), and headache (26%). There was a numerical increase in the number of pulmonary emboli reported in patients receiving palbociclib compared to letrozole alone (Study 1003) or placebo plus fulvestrant (Study 1023). With the exception of hematologic toxicities, most adverse reactions were Grade 1 or 2, and rates of treatment discontinuation for adverse reactions were generally low. No new safety concerns have been identified based on the safety data submitted in this sNDA.	The safety profile of palbociclib plus fulvestrant for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care.
Risk Management	• There is no proposal for a risk management plan.	None

2 Therapeutic Context

Analysis of Condition

Endocrine therapy options for postmenopausal women with HR-positive MBC that do not respond to first line therapy include aromatase inhibitors (anastrozole, letrozole and exemestane), fulvestrant or tamoxifen. Endocrine therapy options for premenopausal women with HR-positive MBC that do not respond to first line therapy are similar to those for postmenopausal women; however, aromatase inhibitors or fulvestrant need to be administered in combination with ovarian suppression therapy. Pre- and postmenopausal women may also receive chemotherapy as second or later lines of treatment, once they have had tumor progression on endocrine therapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options (10,11).

2.2. Analysis of Current Treatment Options

Multiple endocrine and chemotherapy agents have been approved for treatment of MBC. The table below (Table 1) is a summary of FDA-approved available therapies for patients with locally advanced or metastatic breast cancer who have progressed through at least one line of therapy.

Table 1. Available Therapies for Patients with Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Drug Class
Letrozole	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	1997	2.5mg daily by mouth	Vs tamoxifen TTP: 9.4 months vs 6.4 months HR 0.72 (p<0.0001) OS: 35 months vs 32 months (p=0.5136)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Exemestane	Treatment of advanced breast cancer in	1999	25mg daily by mouth	Vs megestrol acetate TTP: 20.3 weeks vs 16.6 weeks (HR	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor

	postmenopausal women whose disease has progressed following tamoxifen therapy			0.84)		
Everolimus	postmenopausal women with advanced HR+, HER2negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.	2012	10mg daily by mouth	Vs exemestane ORR: 12.6% vs. 1.7% PFS: 11.0 months vs. 4.1 months HR=0.38 (p<0.0001) (independent review); 7.8 months vs. 3.2 months HR=0.45 (p<0.0001); (investigator assessed)	Infections, non-infectious pneumonitis, oral ulceration, angioedema, renal failure, impaired wound healing, diarrhea	mTOR inhibitor
Paclitaxel	After failure of initial chemotherapy in MBC	1994	175 mg/m^2 intravenously every 3 weeks	Data from 83 patients accrued in three Phase 2 open label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of paclitaxel in patients with MBC. ORR: 26% (175 mg and 135 mg combined) PFS: 3.5 months	Neuropathy, hepatic toxicity, myelosuppression, hypersensitivity	Microtubule stabilizing agent
Docetaxel	In the treatment of locally advanced or MBC after chemotherapy failure	1996	60 mg/m^2 to 100 mg/m^2 intravenously every 3 weeks	Vs mitomycin/vinblastine ORR: 28.1% vs. 9.5% (p<0.0001) TTP: 4.3 vs. 2.5 (p=0.01)	Fluid retention, neuropathy, hepatic toxicity, myelosuppression, hypersensitivity	Microtubule stabilizing agent
Nab-paclitaxel	In the treatment of MBC after failure of combination chemotherapy	2005	260mg/m2 intravenously every 3 weeks	Vs paclitaxel ORR: 21.5% vs. 11.1% (p=0.003)	Myelosuppression, neuropathy,	Microtubule stabilizing agent

	for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.					
Capecitabine	As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen	1998	1250 mg/m2 twice daily orally for 2 weeks followed by a one week rest period in 3-week cycles	ORR: 18.5 (all); 25.6 (subgroup) PFS: 3 months for all	Coagulopathy, hand foot syndrome, diarrhea, cardiac toxicity,	Oral prodrug of 5'-DFUR to 5-FU
	In combination with docetaxel after failure of prior anthracycline containing therapy for MBC	2001	1250 mg/m2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m2 as a 1-hour IV infusion every 3 weeks	Vs docetaxel alone ORR: 32% vs. 22% PFS: 6.2 months vs. 4.3 months		

HR=hormone receptor; MBC=metastatic breast cancer

Reviewer comment: *The treatment of patients with metastatic breast cancer is palliative in nature. Patients with metastatic HR-positive, HER2-negative breast cancer may be treated with another endocrine therapy once they have had progression of disease on a prior endocrine therapy or with single agent or combination chemotherapy. This decision to use endocrine therapy or chemotherapy is based on several factors. These factors include, but are not limited to, tumor burden of disease, symptoms from the disease, toxicity from previous therapy, patient comorbidities, patient performance status and patient preference.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fulvestrant was approved by the US FDA in 2002 for the treatment of HR-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

3.2. Summary of Presubmission/Submission Regulatory Activity

August 19, 2015: A Type B meeting with AstraZeneca was held to discuss a reverse parallel labeling extension for fulvestrant on the basis of PALOMA-3 to ensure consistency across the labeling for fulvestrant and palbociclib.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) audit was requested for this sNDA. The OSI inspected the one site that accrued the highest number of patients in the United States. A summary of the site inspection is provided in Table 2.

Table 2. OSI Findings in Study 1023

Inspection	Site #, and # of Subjects	Inspection Date	Interim Classification
Dr. Dennis Slamon UCLA Medical Center Los Angeles, CA, USA	Site #: 1137 # of subjects: 14	January 14-28, 2016	VAI. No major issues

VAI=Voluntary Action Indicated

The preliminary classification (based on information in 483 and preliminary communication with inspector) for this inspection site was voluntary action indicated (VAI). 19 subjects were screened at Site 1137 and 14 were enrolled. Records for all 14 enrolled subjects were reviewed. A summary of issues found at Site 1137 are listed below:

- 3 subjects had one or more tumor assessment scan performed out of window between 1 and 28 days.
- 4 subjects failed to complete one or more health-related quality of life and health status

using protocol specified questionnaires.

- 5 subjects' records revealed some discrepancies between source and case report forms (CRF)s pertaining to adverse event (AE)s. Most were Grade1/2 and had start dates and end dates in source/AE logs, but were listed as ongoing in eCRFs.

See Clinical Inspection Summary written by Lauren Iacono-Connors, Ph.D, Good clinical Practice Assessment Branch, Division of Good clinical Practice Compliance, OSI for full details.

Reviewer Comments: *Based on preliminary inspectional findings, data submitted to the Agency from Site 1137 appear reliable. It is unlikely that any of the issues found at Site 1137 impacted subject safety or study outcome analysis.*

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable. See original NDA.

4.5. Clinical Pharmacology

Not applicable. See original NDA.

4.5.1. Mechanism of Action

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor. See original NDA for further details.

4.5.2. Pharmacodynamics

Not applicable. See original NDA.

4.5.3. Pharmacokinetics

Not applicable. See original NDA.

4.6. Devices and Companion Diagnostic Issues

No companion device or diagnostic is included in this application.

4.7. Consumer Study Reviews

Not applicable to this sNDA.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary evidence to support this supplement application is derived from Study 1023 as seen in Table 3.

Table 3. Listing of Clinical Trials Relevant to this sNDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
A5481023	Randomized, double-blind phase 3 study	Palbociclib 125mg daily for 3 weeks on 1 week off with fulvestrant 500mg days 1,15,29 and monthly thereafter vs fulvestrant plus placebo (at same dose listed above)	Investigator assessed PFS	Median days on treatment: palbociclib-144, fulvestrant-148 vs fulvestrant-128,placebo-120	571	Women with HR+, HER2 negative advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy	144 centers in 17 countries

5.2. Review Strategy

The efficacy review was conducted by Dr. Suparna Wedam and the safety review by Dr. Amanda Walker. As per a signed data sharing agreement between Pfizer and AstraZeneca, data from Study 1023 is cross-referenced in this sNDA. Additionally a literature review regarding efficacy of palbociclib monotherapy was conducted.

6 Review of Relevant Individual Trials Used to Support Efficacy

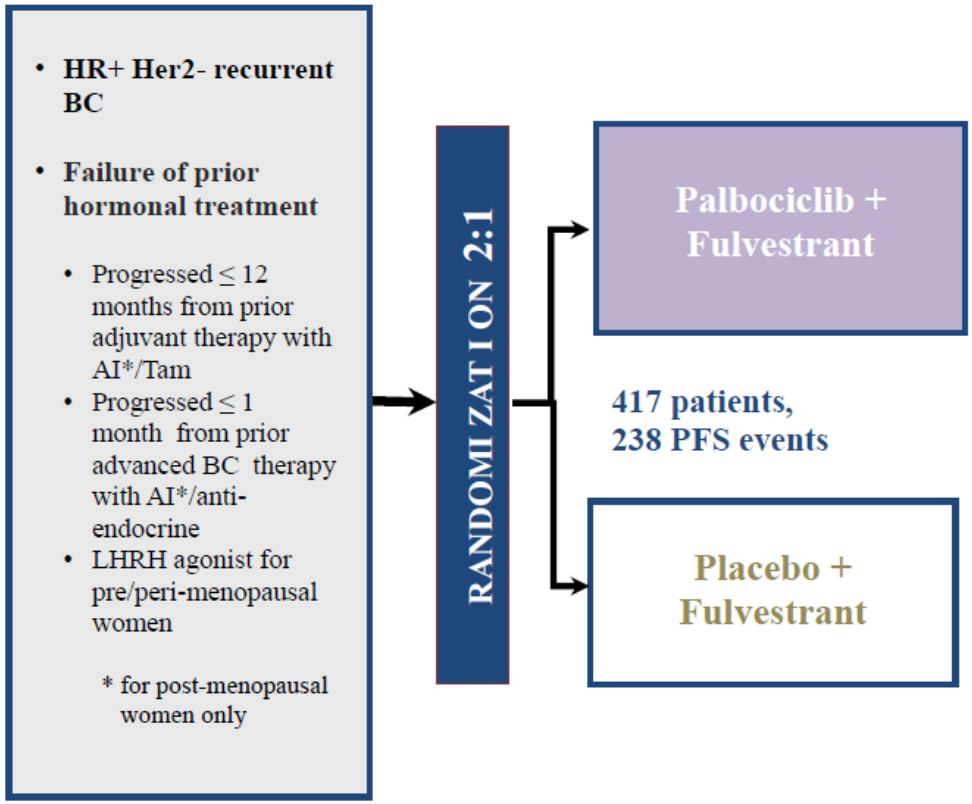
A5481023 (Study 1023 or PALOMA-3)

6.1.1. Study Design

Overview and Objective

This sNDA contains data from Study 1023, entitled "Multi-center, randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant (Faslodex®) with or without PD-0332991 (Palbociclib) +/- goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy"(Figure 1). Patients were treated with either palbociclib 125 mg/day or placebo orally for 3 of 4 weeks. Patients also received fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and every 28 days thereafter starting from Day 1 of Cycle 1. In both arms, pre- and peri-menopausal women also received the LHRH agonist goserelin (Zoladex® or generic). The primary objective was to demonstrate an improvement in investigator-assessed progression free survival with palbociclib plus fulvestrant over fulvestrant alone. Key secondary objectives include overall survival, objective response rates, duration of response, and clinical benefit response (CR or PR or SD ≥ 24 weeks).

Figure 1. 1023 Study Design



Patients on either arm were allowed to continue treatment after initial investigator-assessed RECIST v 1.1-defined progression if it was considered to be in the best interest of the patient and no new anticancer treatment was initiated. Cross-over between arms was not permitted.

Choice of Control Group

Fulvestrant is a potent anti-estrogen drug that binds and degrades ER and is currently indicated for the treatment of postmenopausal women with metastatic HR-receptor positive breast cancer following the failure of anti-estrogen therapy. The Applicant chose fulvestrant as the comparator arm due to its significant antitumor activity in patients whose tumors had progressed after anti-estrogen or AI therapy.

Diagnostic Criteria

Patients were required to have histologically or cytologically proven hormone receptor positive, HER2 negative breast cancer with evidence of metastatic or locally advanced disease that is not amenable to therapy with curative intent. The documentation of an ER-positive and/or PR-positive and HER2 negative tumor must be based on the most recent tumor biopsy (unless bone only disease) utilizing an assay consistent with local standards. Hormone receptor positivity is defined as ≥ 1% positive stained cells, and HER2-negativity is defined as an immunohistochemistry score 0/1+ or negative *by in situ* hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio < 2 or a HER2 copy number < 4 for a single probe assessment.

Reviewer comment: *The Agency recommends the documentation of ER, PR, and HER2 status using an assay consistent with central standards.*

Inclusion/Exclusion Criteria

Inclusion Criteria:

- Women 18 years of age or older who are either:
  - Post-menopausal, as defined by at least one of the following:
    - Age ≥ 60 years;
    - Age < 60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and FSH level within the laboratory's reference range for postmenopausal females;
    - Documented bilateral oophorectomy;
    - Medically confirmed ovarian failure

OR

- Pre/perimenopausal (i.e. not meeting the criteria for being postmenopausal).
  - Pre/perimenopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to randomization. But, if patients have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial.

- Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
- Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (unless bone-only disease, see below) utilizing an assay consistent with local standards.
- Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.
- Patients must satisfy the following criteria for prior therapy:
  - Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal.

  OR

  - Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or perimenopausal. One previous line of chemotherapy for advanced/metastatic disease is allowed in addition to endocrine therapy.
- Except where prohibited by local regulations, all patients must agree to provide and have available a formalin-fixed paraffin embedded (FFPE) tissue biopsy sample taken at the time of presentation with recurrent or metastatic disease. A de novo biopsy is required if no archived tissue taken at the time of presentation with recurrent/metastatic disease is available. The sole exception is those patients with bone only disease for whom provision of previous archival tissue only is acceptable. Patients who had surgery within the last 3 years (but without neoadjuvant chemotherapy prior to surgery) and relapsed while receiving adjuvant therapy may provide a tumor specimen from that surgery.

- Measurable disease as defined by RECIST v 1.1, or bone-only disease. Patients with bone-only metastatic cancer must have a lytic or mixed lytic-blastic lesion that can be accurately assessed by CT or MRI. Patients with bone-only disease and blastic-only metastasis are not eligible.
- Patients must satisfy the following criteria for prior therapy:
    - Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal.

      OR
    - Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or perimenopausal. One previous line of chemotherapy for advanced/metastatic disease is allowed in addition to endocrine therapy.
- ECOG performance status 0-1.
- Adequate organ and marrow function defined as follows:
    - ANC ≥1,500/mm3 (1.5 x 109/L);
    - Platelets ≥100,000/mm3 (100 x 109/L);
    - Hemoglobin ≥9 g/dL (90 g/L);
    - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≤60 ml/min as calculated using the method standard for the institution;
    - Total serum bilirubin ≤1.5 x ULN (<3ULN if Gilbert's disease);
    - AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);
    - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN if bone or liver metastases present).
- Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) CTCAE Grade ≤1 (except alopecia).
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.
- Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

- Prior treatment with any CDK inhibitor, or fulvestrant, or with everolimus, or any agent whose mechanism of action is to inhibit the PI3K-mTOR pathway.
- Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).
- Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
- Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers, and drugs that are known to prolong the QT interval.
- Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to ☐25% of bone marrow are n
- Any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
- QTc interval > 480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes.
- Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.
- Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of palbociclib, such as history of GI surgery with may result in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE Grade >1.
- Prior hematopoietic stem cell or bone marrow transplantation.
- Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or goserelin (if applicable).
- Known or possible hypersensitivity to fulvestrant, goserelin, any of their excipients or to any palbociclib/placebo excipients.
- Known human immunodeficiency virus infection.

- Other severe acute or chronic medical or psychiatric condition, including recent or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
- Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.
- Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before randomization in the current study.

Reviewer's comments: *Overall, the inclusion/exclusion criteria are appropriate. Of note, men with breast cancer were not eligible for Study 1023.*

Concomitant Radiotherapy or Surgery:

Concurrent radiotherapy or cancer-related surgery was prohibited throughout the duration of the active treatment phase of the study. Palliative radiotherapy was permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. Palliative radiotherapy of any other site was considered alternative cancer treatment resulting in censoring of the PFS endpoint. Caution was advised for any surgical procedures during the study.

Dose Selection

The Applicant chose the palbociclib dose regimen of 125 mg/day for 3 of 4 weeks based upon the results of a Phase I dose escalation study (A5481001). Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on/1 week off) and Schedule 2/1 (2 weeks on/1 week off). A greater proportion of patients on the 2/1 schedule had treatment-related TEAEs than patients on the 3/1 schedule, and a total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD) including 6 patients with SD lasting 40 weeks or longer. Based on the relatively improved safety profile of Schedule 3/1 and the efficacy results from this study, the Schedule 3/1 was selected for further clinical development. The RP2D for this study schedule was determined to be 125 mg/day. This dose and schedule of palbociclib was further explored in combination with letrozole in a phase 1/2 study (A5481003)

which led to accelerated approval of palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

The 500 mg dose of fulvestrant was used in Study 1023 in combination with palbociclib and placebo given the favorable safety profile and efficacy results of the CONFIRM study, a Phase 3 study that compared two doses of fulvestrant (250 mg and 500 mg). The median PFS was 6.5 months for fulvestrant 500 mg and 5.5 months for fulvestrant 250 mg; a statistically significant difference in favor of the higher dose (HR=0.80; 95% CI: 0.68 0.94; p=0.006).

Study Treatments

Arm A (Investigational Arm):

- Palbociclib capsules of 75 mg, 100 mg, and 125 mg.
    - Starting Dose: 125 mg daily for 21 days followed by 7 days off treatment of each 28-day cycle (3/1 schedule)
    - Palbociclib doses could be reduced to 100 mg daily and 75 mg daily on 3/1 schedule, respectively, or to 75 mg on a 2-week on/2-week off (2/2) schedule.
    - Administration: oral
    - Pfizer Lot Numbers
        - 75 mg capsules: 13-109348, 13-107814, 13-111143
        - 100 mg capsules: 13-107411, 13-109347, 13-111139
        - 125 mg capsules: 13-1007781, 13-109759, 13-109346, 13-111134

In Combination With

- Fulvestrant 250 mg/5 mL syringe solution for injection
    - Dose: 500 mg on Days 1 and 15 of Cycle 1, thereafter every 28 ±7 days every cycle, starting on Day 1 of Cycle 1, according to approved fulvestrant prescribing information.
    - Administration: IM
    - Pfizer Lot Numbers: 13-110227, 13-109742, 14-001237, 13-109468, 14-002736, and 13-110724

Arm B (Comparator arm):

- Palbociclib capsule-matched placebo

- Starting Dose: 125 mg palbociclib-matched placebo daily for 21 days followed by 7 days off treatment of each 28-day cycle (3/1 schedule). Palbociclib-matched placebo doses could be reduced to 100 mg daily and 75 mg daily on 3/1 schedule, respectively, or to 75 mg on a 2-week on/2-week off (2/2) schedule.
- Administration: oral
- Pfizer Lot Numbers: 12-004486, 12-004533, and 12-004572

In Combination With

- Fulvestrant as described above.

Pre- and perimenopausal women started receiving goserelin or an alternative LHRH agonist at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered every 28 days during the active treatment phase.

Reviewer's comment: *The dose and schedule of fulvestrant and goserelin is appropriate. Based on prior studies with palbociclib, the dose and schedule of palbociclib is appropriate.*

Assignment to Treatment:

Patients were randomized using a centralized internet/telephone registration system no more than 4 business days before administration of the first dose of investigational agent. After informed consent was obtained, the clinical site completed a patient pre-randomization form (which included key eligibility criteria and stratification factors) and sent it to the sponsor for approval of randomization. Upon receipt of the sponsor's approval, the site was to contact the centralized internet/telephone registration system for randomization. Subjects were randomly assigned on a 2:1 basis to receive palbociclib plus fulvestrant or placebo plus fulvestrant. Subjects were stratified by documented sensitivity to prior hormonal therapy (yes vs. no), menopausal status at study entry (pre/peri- vs. post-menopausal), and presence of visceral metastases (yes vs. no). Sensitivity to prior hormonal therapy is defined as either: (i) documented clinical benefit (CR, PR, SD ≥ 24 weeks) to at least one prior hormonal therapy in the metastatic setting, or (ii) at least 24 months of adjuvant hormonal therapy prior to recurrence. "Visceral" refers to lung, liver, brain, pleural and peritoneal involvement. There were no plans to change the randomization during the study.

Blinding

Palbociclib and placebo were provided by the Applicant and supplied as indistinguishable capsules matching in size and color. Blinding codes were only broken in emergency situations for reasons of patient safety. Blinding codes could also be broken after a patient discontinued treatment due to disease progression, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion in agreement with the sponsor. When the blinding code was broken, the date and reason for unblinding was required to be fully documented in source documents and entered on the case report form and every effort made by the site staff to ensure that the treatment arm is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

Reviewer's comment: *The hematologic toxicities of palbociclib likely prevented investigator blinding.*

Dose Modifications

In the event of significant treatment-related toxicities, dose adjustments were permitted for palbociclib/placebo only. Fulvestrant dose adjustments were not allowed; however, dosing delays or interruptions were permitted according to standard practice. When treatment interruption was deemed necessary for just one of the study drugs in the combination, treatment with the other study drug was continue as planned.

In the case of Grade 2 toxicity lasting for > 3 weeks or a Grade ≥ 3 toxicity, dose reduction of palbociclib was recommended for the subsequent cycles. Dose reduction by one, and, if needed, two dose levels was recommended depending on the type and severity of the toxicity. Available dose levels are shown in Table 1 below.

Table 4. Palbociclib Dose Levels

Dose Level	Palbociclib/Placebo for 3 out of 4 weeks (3/1 schedule)	Fulvestrant monthly dosing schedule
Starting dose	125 mg/d	2x 250 mg/injection
-1	100 mg/d	2x 250 mg/injection
-2	75 mg/d*	2x 250 mg/injection

* Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed, but the schedule may be changed to 75 mg/day two weeks on followed by two weeks off (2/2 schedule).

Patients requiring more than two dose reductions were allowed to receive 75 mg/day for 2 weeks followed by 2 weeks off. Once a dose was reduced for a given patient, all subsequent cycles were administered at that dose level, unless further dose reduction is required. Dose re-escalation was not permitted. The pre-specified dose reductions for various treatment-related toxicities are shown in Table 2 below.

Table 5. Palbociclib/Placebo Dose Modifications for Treatment-Related Toxicities

Toxicity	**Palbociclib/Placebo Treatment at:**
Uncomplicated Grade 3 neutropenia *(ANC ≥ 500 - <1000/mm^3)*	Same dose level; ↓ 1 dose level if neutrophil recovery is delayed beyond 7 days *, **
Grade 3 neutropenia (*ANC<1000/mm^3*) **associated with a documented infection or fever ≥38.5 degrees C**	↓ 1 Dose Level; ↓ 2 dose levels*** if neutrophil recovery is delayed beyond 7 days *
Grade 4 neutropenia (*ANC<500/mm^3*)	↓ 1 Dose Level; ↓ 2 dose levels*** in case of recurrent grade 4 event *
Grade 3 or 4 thrombocytopenia (*Platelet count <50,000/mm^3*)	↓ 1 Dose Level; ↓ 2 dose levels*** in case of recurrent grade 3 event
Grade ≥ 3 non-hematologic toxicity (*including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment*)	↓ 1 Dose Level; ↓ 2 dose levels***, if repeated toxicity is seen in the next cycle or if recovery from grade 3 is delayed beyond 7 days *

* If recovery of neutrophils to ≥ 1000/mm^3 or platelet count to ≥ 50,000/mm^3 takes longer than 2 weeks (which may include dose holding due do toxicity, the scheduled week off treatment and up to 7 days of cycle delay), then reduce by 2 dose levels.

** If uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles, after recovery as per retreatment criteria (ANC ≥ 1000/mm^3 and no fever), treatment may restart at the next lower dose level at investigator's discretion.

*** If no further dose reduction is possible (ie, patient is already receiving 75 mg/d according to schedule 3/1) consider changing the schedule to 75/mg/d 2 weeks on/2 weeks off), or discontinue palbociclib/placebo and continue with fulvestrant alone.

Administrative Structure:

The applicant utilized an independent External Data Monitoring Committee (E-DMC) for general oversight of safety and efficacy considerations, study conduct, and risk-benefit assessment of this study. The E-DMC acted in an advisory capacity to the sponsor, monitoring patient safety and evaluating available efficacy data for the study. The sponsor designated a biostatistician not affiliated with the project to prepare data for E-DMC review.

A sample-based blinded independent central review (BICR) was used as an auditing tool for PFS in order to corroborate the analysis results of the primary endpoint (i.e., investigator-assessed PFS) and to assist in the evaluation of potential bias.

Procedures and Schedule

The key assessments and procedures for this study were:

Screening

- Eligibility assessment
- Informed consent
- Laboratory tests
- Physical examination including ophthalmic exam
- Baseline tumor assessment
- EKG
- Tumor tissue for biomarker analysis

- PK analysis
- Patient reported outcome measurements

On-study

- Laboratory tests
- Tumor assessments every 8 weeks (+/- 7 days) for the first year, and then every 12 weeks (+/- 7 days) from the date of randomization
- Adverse events assessment
- PK analysis
- Patient reported outcome measurements

Follow-up

- Adverse events followed until 28 days after discontinuation of study treatment (either palbociclib/placebo or fulvestrant).
- In patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumor assessments every 8 weeks) for the first year, and then every 12 weeks from the date of randomization until documented progression or onset of new anticancer therapy.
- For patients who discontinue study treatment due to objective disease progression, survival data (i.e., patient status along with start, stop and type of new anticancer therapy) will be collected every 3 months for the first 9 months then every 6 months starting at Month 15, calculated from the last dose of study treatment.

  A detailed schedule of activities is shown in Table 6 below.

Table 6. Schedule of Activities

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 28 days			End of Treatment/Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2		Cycles ≥3		
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 [b]	Day 15	Day 1		
Visit Window		±-2 days	±2 days	±7 days [a]		±7 days
Informed Consent [e]	X					
Medical/Oncological History [f]	X					
Baseline Signs/Symptoms [g]		X [g]				
Physical Examination/Vital Signs [h]	X	X [b]		X	X	
Ophthalmic Examination[i]	X			X [i]	X	
ECOG Performance Status	X	X		X	X	
Laboratory Studies						
Hematology [j]	X	X [b]	X	X	X	
Blood Chemistry [j]	X	X [b]	X	X	X	
Pregnancy test, serum estradiol and FSH (if applicable) [j]	X					
12-Lead ECG (in triplicate)	X				X	
Disease Assessment						
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease [k]	X	◄--► [k] Performed every 8 weeks (±7 days) for the first year, and then every 12 weeks (±7 days) from the date of randomization (See tumor assessment requirements flowchart)			X	X
Radionuclide Bone Scan, Whole Body [l]	X	As clinically indicated or to confirm complete response. (See tumor assessment requirements flowchart) [l]			X	X

Protocol Activity	Screening	Active Treatment Phase [a] - One Cycle = 28 days			End of Treatment/Withdrawal [c]	Post-Treatment Follow-Up [d]
		Cycles 1 and 2		Cycles ≥3		
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 [b]	Day 15	Day 1		
Visit Window		±-2 days	±2 days	±7 days [a]		±7 days
Other Clinical Assessments						
Adverse Event Reporting [m]	X	X	X	X	X	X
Concomitant Medications/Treatments	◄--► Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment					
Pharmacokinetics (PK) [n]		First 40 patients: Sampling at pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3; all other patients: Pre-dose sampling on Day 15 of Cycles 1 and 2				
Banked Blood Biospecimens (Prep D1) [o]		X				
Plasma banking (Prep B1) [p]		X	X		X	
Tumor Tissue for Biomarker Analysis [q]	X				X	
EuroQol-5D (EQ-5D) [r]		Pre-dose on Day 1 of Cycles 1, 2, 3, 4 and Day 1 of every other cycle thereafter starting with Cycle 6 (ie, Cycle 6,8, 10, etc)			X	
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) [r]					X	
European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC-QLQ-BR23) [r]					X	
Survival Follow-up [s]						X
Study Treatment						
Randomization		X				
Fulvestrant (both treatment arms) [t]		◄--►[t] IM administration on Days 1 and 15 of Cycle 1, every 28 days (±7 days) thereafter starting from Day 1 of Cycle 1				
Palbociclib or placebo (Arm A only) [u]		◄--►[u] Orally once daily on Days 1 to 21of each Cycle followed by 7 days off treatment				
For pre-/peri-menopausal patients only: Goserelin (both treatment arms, if applicable) [v]	SC administration at least 4 weeks before study treatment start [v]	◄--►[v] SC administration every 28 days				

a. **Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. A cycle could be longer than 28 days if persistent

toxicity delays initiation of the subsequent cycle. **Day 1 of any cycle visit should coincide with the day the palbociclib/placebo treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows). Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). The active treatment phase is ongoing as long as the patient is receiving both study drugs (ie, palbociclib/placebo and fulvestrant) or fulvestrant alone.

b. **Cycle 1/Day 1:** Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.
c. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).
d. **Post Treatment Follow-up:** Patients who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment (palbociclib/placebo or fulvestrant) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. Telephone contact is acceptable. Patients who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumor assessments performed every 8 weeks (±7 days) for the first year, and then after 1 year every 12 weeks (±7 days) (calculated from the date of randomization) until documented progression or onset of new anticancer therapy. See Tumor Assessment Requirements Flowchart for details. For patients who discontinue study treatment due to objective disease progression, see table footnote s (Survival Follow-up) below.
e. **Informed Consent:** Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Screening Section).
f. **Medical/Oncological History:** To include information on prior anticancer treatments.
g. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the Cycle 1 Day 1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
h. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. Physical examinations will be carried out at Screening, Day 1 of every cycle and the End of Treatment/Withdrawal visit.
i. **Ophthalmology Examinations:** Upon approval of Amendment 1, newly enrolled lens grading evaluable patients will undergo an ophthalmic examination by an ophthalmologist at screening, during study treatment on Cycle 4 Day 1, on Cycle 7 Day 1, on Cycle 13 Day 1 (ie, after 3, 6 and 12 months), every 12 months thereafter (ie, Days 1 of Cycles 25, 37, etc.) and at the End of Treatment/Withdrawal visit. Additional ophthalmic examinations may be performed as clinically indicated. It is expected that a minimum of 100 evaluable patients will participate in these examinations. Sites will be informed once these examinations are no longer required for patients newly enrolled in this study. Refer to the Ocular Safety Assessments Section for further details.
j. **Laboratory tests:** Hematology includes hemoglobin, WBC, absolute neutrophil count, platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN) (or urea), serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. Upon approval of Amendment 2, hemoglobin A1c will be measured in all patients every 3 months from the date of randomization (ie, C4D1, C7D1, C10D1, etc), and at the End of Treatment/Withdrawal visit. Pregnancy test (serum) at screening only for women of childbearing potential. Test may be repeated as per request of IRB/IECs or if required

by local regulations. Serum estradiol and Follicle stimulating hormone (FSH) levels are analysed at screening to confirm postmenopausal status of women <60 years old and who have been amenorrheic for at least 12 consecutive months.

k. **CT/MRI Scans of Chest, Abdomen, Pelvis:** Refer to the tumor assessment requirement flowchart for details and timing of procedures
l. **Radionuclide Bone Scan, Whole Body:** Refer to the tumor assessment requirement flowchart for all details and timing of procedures.
m. **Adverse Events (AEs):** Serious Adverse events (SAEs) must be reported from the time the patient provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. All AEs (serious and non serious) should be recorded on the CRF from the first dose of study treatment through last patient visit. It is expected that telephone contact with the patient will be made in order to assess SAEs and AEs 28 calendar days (+/- 7 days) after the last administration of the study drug.
n. **Pharmacokinetics (PK)**: In approximately the first 40 patients randomized in the study, plasma PK samples will be drawn pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3 for DDI assessment for palbociclib and fulvestrant (and goserelin if applicable). In all other patients, plasma concentrations will be drawn on Day 15 of Cycle 1 and Cycle 2 for palbociclib only. Additional PK blood samples may be collected from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.
o. **Banked Blood Biospecimens (Prep D1):** A single 4 mL blood sample will be collected pre-dose at the Cycle 1 Day 1 to be retained for potential pharmacogenomics/biomarker analyses related to drug response or adverse drug reactions. Samples will be collected from all patients, unless prohibited by local regulations.
p. **Plasma Banking (Prep B1):** Blood samples for plasma collection (2x 10 mL each) will be drawn for exploratory analyses from all patients pre-dose on Cycle 1 Days 1 and 15 and at End of Treatment/Withdrawal, unless prohibited by local regulations.
q. **Tumor Tissue for Biomarker Assessments:** Tumor tissue is required for patient participation, and patients must agree to provide tissue from the metastatic or recurrent site at the time of study entry. For the purpose of eligibility, documentation of ER-positive and/or PR-positive tumor and HER2-negative tumor will be based on local results utilizing an assay consistent with local standards. Archived formalin-fixed paraffin embedded (FFPE) specimen will be collected. If archived metastatic or recurrent tumor FFPE specimen is not available, a de novo biopsy will be required for patient participation, except for those with bone disease only who will need to provide the original diagnostic FFPE tumor specimen. Patients who relapsed while receiving adjuvant therapy and had surgery within the last 3 years, may provide a tumor specimen from that surgery. Provision of new metastatic tissue from these patients is strongly encouraged but not mandated. An optional de novo tumor biopsy will be collected from the site of progression at the End of Treatment visit. Details on sample preparation, processing, storage, and shipment will be provided in the Study Manual.
r. **Patient Reported Outcomes Assessments:** All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in clinic may be used under special circumstances.
s. **Survival Follow-Up:** For patients who discontinue study treatment due to objective disease progression, survival data (ie, patient status along with start, stop and type of new anticancer therapy) will be collected every 3 months for the first 9 months (Month 3, 6, and 9, ±14 days), then every 6 months starting at Month 15 (±14 days), calculated from the last dose of study treatment. Telephone contact is acceptable.
t. **Fulvestrant:** To be administered on-site according to the local Summary of Product Characteristics for fulvestrant (Faslodex®). Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows).

u. **Palbociclib or Placebo:** Patients will be required to return all bottles of palbociclib/placebo as well as the completed patient diary on Day 1 of each cycle for drug accountability.

v. **Goserelin (if applicable):** Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). Treatment with goserelin (Zoladex® or generic) as per local practice for all women who are pre- or peri-menopausal at study entry. Patients must have commenced treatment with goserelin or an alternative luteinizing hormone-releasing hormone (LHRH) agonist at least 4 weeks prior to randomization. If patients have not received goserelin as their LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial. It is recommended to administer goserelin (given every 28 days) on-site when monthly fulvestrant is given. If goserelin is administered at home by the patient, a patient diary will be implemented.

Reviewer comment: *There is preclinical evidence to suggest that the occurrence of ocular toxicities in patients receiving palbociclib may be related to altered glucose metabolism. However, serum glucose measurement was not reported in Study 1023. In order to further explore this association, the protocol was amended in September 2014 to include the measurement of HgbA1c.*

Concurrent medications

Prohibited concurrent medications include anticancer agents, potent (strong/moderate) CYP3A inhibitors/inducers, drugs known to cause QT interval prolongation, hormone replacement therapy, megastrol acetate, selective estrogen-receptor modulators, anticoagulants, and proton-pump inhibitors. The initial protocol was amended based on preliminary results from two clinical pharmacology studies (A5481018 and A5481021) which suggested that palbociclib exposure may be decreased in a subgroup of patients taking with proton-pump inhibitors.

Treatment compliance

Treatment compliance was monitored by drug accountability as well as the patient's treatment diary and medical record. Drug accountability was performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. To be considered compliant, each study patient must have received at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration during the study. Fulvestrant was administered by qualified study personnel at the site in accordance with the fulvestrant label. Fulvestrant administration was documented on the corresponding study drug administration CRF.

Rescue medication

Primary prophylactic use of granulocyte-colony stimulating factors was not permitted but may have been used in the context of treatment-emergent neutropenia. If neutropenic complications were observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered a reasonable alternative. Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

Subject completion, discontinuation, or withdrawal

The term "discontinuation" refered to a patient's withdrawal from the active treatment phase, i.e., discontinues treatment of palbociclib/placebo AND fulvestrant. Patients may Have been withdrawn from the active treatment phase in case of disease progression, symptomatic deterioration, need for new or additional anticancer therapy not specified in the protocol, unacceptable toxicity, investigator's conclusion that discontinuing therapy is in the patient's best interest, lost to follow-up, patient choice to withdraw from treatment (follow-up

permitted by patient), withdrawal of patient consent (cessation of follow-up), or death. Patients who discontinued from the active treatment phase must have had end of treatment/withdrawal evaluations performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Data collected for the end of study treatment/withdrawal are described the schedule of activities in Table 3. Patients were to be withdrawn from study in the case of withdrawal of patient consent (i.e. refuses tumor assessments or follow-up on survival status after the end of treatment), lost to follow-up, or death.

Study Endpoints

The primary endpoint of Study 1023 was investigator-assessed progression-free survival (PFS), defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS data was censored on the date of the last tumor assessment on study for patients who did not have objective tumor progression and who did not die while on study. Patients lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with the duration of one day. Additionally, patients who started a new anti-cancer therapy prior to documented PD were censored at the date of the last tumor assessment prior to the start of the new therapy. Patients with documentation of PD or death after an unacceptably long interval (i.e., 2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD. The primary analysis was performed in the ITT population.

Secondary endpoints include:

- Overall Survival (OS)
- 1-year, 2-year, and 3-year survival probabilities
- Objective Response (OR: CR or PR)
- Duration of Response (DR)
- Clinical Benefit Response (CBR: CR or PR or SD ≥ 24 weeks)
- Type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), seriousness and relationship to study medications of AEs and any laboratory abnormalities. AEs were coded using the MedDRA version 17.1)
- Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable) in the subgroup of approximately 40 patients included in the initial safety assessment
- PRO endpoints such as health related quality of life scores [EuroQol (EQ-5D) Score; European Organization for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-C30); European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ-BR23); minimally important difference (MID) cut-off, and time to deterioration (TTD) composite endpoint
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1 and

CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6)

Efficacy analyses were performed using the local radiologist's/investigator's tumor assessments as the primary data source. Additionally, an independent third-party core imaging laboratory, (b) (4), performed blinded independent central review (BICR) of PFS data for a randomly selected subgroup of patients independent of the investigator assessed determination of progression.

Statistical Analysis Plan

The sample size for this study was determined based on the results of the randomized Phase 2 trial assessing fulvestrant with or without dasatinib in postmenopausal patients with HR-positive metastatic breast cancer previously treated with an aromatase inhibitor. The median PFS for the fulvestrant alone arm was 5.3 months and the median PFS for the combination arm was 6.0 months. The study planned to randomize 417 patients (278 in the fulvestrant plus palbociclib arm and 139 in the placebo plus fulvestrant arm) in a 2:1 randomization ratio. Approximately 238 PFS events were required in the two treatment arms for the study to have a 90% power to detect an increase in PFS assuming a true HR of 0.64 (representing a 56% increase in median PFS from 6 to 9.38 months), if tested at a 1-sided significance level of alpha=0.025. The null hypothesis was that there is no difference in progression free survival between the palbociclib plus fulvestrant arm and the fulvestrant plus placebo arm.

The primary efficacy analysis population was the intent-to-treat (ITT) population. Patients were to be classified according to assigned treatment group, regardless of actual treatment received. PFS was defined as the time from the date of randomization to the date of the documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever comes first. If tumor progression data included more than one date, the first date was used. Documentation of progression must have been objective disease assessment based on RECIST v1.1. The length of PFS was calculated as PFS time (months) = [progression/death date (censor date) – randomization date +1]/30.4.

Censorship: Patients last known to be 1) alive 2) not to have started new (non-protocol) anti-cancer treatment and 3) progression-free, and who have a baseline and at least one disease assessment after dosing, were to be censored at the date of the last objective disease assessment that verified the lack of disease progression.

- Patients with no disease assessments after dosing were to be censored at the date of randomization unless death occurred prior to the first planned assessment (in which case the death is an event).
- Patients starting new anti-cancer treatment prior to progression were to be censored at the date of last objective disease assessment documenting no progression prior to the new treatment.
- If patients were removed from the study (withdrew the consent, lost to follow up, etc)

prior to progression and death, then censorship was to be at the date of the last objective disease assessment that verified lack of disease progression.

- Patients with documentation of progression or death after an unacceptably long interval since the last tumor assessment were to be censored at the time of last objective assessment documenting no progression.

The study was designed to have one interim analysis (IA) and the final analysis at 238 events based on the primary PFS endpoint with the investigator assessment. The IA was to be conducted to allow for early stopping of the study due to efficacy or to potentially re-estimate the sample size of the trial based upon the primary endpoint of PFS. The interim analysis was to be performed after approximately 143 investigator-assessed PFS events. The Haybittle-Peto efficacy boundary was to be used at the IA. If the value of the test-statistic from the log-rank test for PFS exceeds the efficacy boundary ($z \geq 3$, $p \leq 0.00135$) the trial may have been stopped for efficacy.

Overall survival (OS) was defined as the time from date of randomization to date of death due to any causes. OS was to be hierarchically tested for significance at the time of PFS analyses, provided the primary PFS endpoint is statistically significant at the interim and/or final PFS analyses. A stratified log-rank test (using the same stratification factors as for the PFS analysis) was to be used to compare OS between the treatment arms. OS for the two treatment arms was to be assessed using Kaplan-Meier methods and displayed graphically where appropriate. Cox regression models were to be used to estimate the treatment hazard ratio and its 95% CI. The 1-year survival probability was to be estimated using the Kaplan-Meier method and a two sided 95% CI for the log [-log(1-year survival probability)] calculated using a normal approximation using the Greenwood's formula, and then back transformed to give a CI for the 1-year survival probability itself. The 2-year and 3-year survival probabilities were to be estimated similarly.

Objective response rate (ORR) was defined as the number of patients with OR (CR or PR per RECIST 1.1) by the number of patient's randomized to the respective treatment arm. A 95% CI for response rates was to be provided. Response rate comparisons between the two treatment arms as randomized were to be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis. Analyses of ORR were to be performed on the ITT population based on the investigator's assessment as well and also on the review of the blinded independent third-party core imaging laboratory. In addition, the Best Overall Response for each patient was to be summarized by treatment arm.

Duration of response (DR) was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. DR data was to be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die due to any cause while on study. DR was to be calculated for the subgroup of

patients with an OR. DR for the two treatment arms was to be summarized using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time and 95% CI for the median was to be provided for each endpoint.

Clinical Benefit Response (CBR) was defined as CR or PR or SD ≥ 24 weeks. The CBR rate on each randomized treatment arm was to be estimated by dividing the number of patients with CR, PR, or SD ≥ 24 weeks by the number of patients randomized to the treatment arm. A 95% CI for the CBR rates was to be provided. CBR rate comparison between the two treatment arms as randomized was to be assessed using CMH test with the same stratification factors as for the PFS analysis. Analyses for CBR were to be performed on the ITT population based on the investigator's assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

The primary safety analysis population was planned to include all patients who received at least one dose of study treatment (i.e. palbociclib/placebo or fulvestrant), with treatment assignments designated according to actual treatment received.

Protocol Amendments

The applicant submitted 2 protocol amendments. Key changes are summarized here:

Amendment 1 (April 4th, 2014): The study drug administration instructions were revised from administration of palbociclib in a fasted state to administration with food and to prohibit the concomitant use of proton-pump inhibitors based on preliminary results from two clinical pharmacology (Studies 1018 and 1021) which suggested that palbociclib taken with food results in more consistent drug absorption and exposure than in a fasted state, and palbociclib exposure may be decreased in a subgroup of patients taking palbociclib concomitantly with proton-pump inhibitors.

Amendment 2 (September 30th, 2014): The protocol was amended in order to prospectively characterize whether or not palbociclib affects glucose metabolism through monitoring of appropriate laboratory measurements given the nonclinical findings in rats and taking into account the limited laboratory glucose data in the current clinical dataset. Prospective monitoring of hemoglobin A1c was added to characterize whether or not palbociclib affected glucose metabolism.

Reviewer's comment: *These amendments did not alter the study's integrity. The applicant's methods for assuring data quality and integrity are appropriate; however, no information was provided in regards to the sponsor's measures to assure complete and accurate identification of protocol deviations.*

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated the study was conducted in accordance with the protocol, the International Conference on Harmonization (ICH) guideline Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

Data Quality and Integrity: Sponsor's Assurance

The Applicant stated that Compliance Oversight Leads (COLs) provided study and site level oversight to ensure that trial was delivered to high quality standards. COLs documented and recorded onsite and remote oversight to assess monitoring effectiveness and ensure compliance with the study protocol by investigational sites according to ICH/ GCP, applicable standard operating procedures (SOPs) and local regulation.

During study conduct, Pfizer or its agent conducted periodic monitoring visits to ensure that the protocol and GCPs were being followed. The monitors reviewed source documents to confirm that the data recorded on CRFs was accurate. The investigator and institution allowed Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. A total of 17 site audits were conducted during this study until the data cut-off date December 5, 2014.

Financial Disclosure

All investigators were assessed for equity interest, significant payments of other sorts, other compensation by the sponsor and propriety interest. Financial disclosure information is provided for covered studies A5481001, A5481003, A5481008, A5481010, A5481023, and A5481034. Of the 3,504 investigators listed, certification was provided for 3,465. Due Diligence activities was required for 1 of the 3,504 clinical investigators. Thirty eight of the 3,504 clinical investigators listed in the study report had financial information to disclose (1.2%).

Study A5481023 (PALOMA-3) included 171 principal investigators and 1061 sub-investigators. Six had financial information to disclose and are summarized in the following table (Table 7).

Table 7. Summary of Financial Disclosures for Study 1023

Clinical Site Number	Investigator Name (PI or SI)	Study A5481023 Patient Enrollment at Site	Disclosure
[redacted]	[redacted]	(b) (6)	Honorariums totaling $26,000.00
			Equity Pfizer totaling $438,498.72 (as of 1/10/2014)
			Consulting and honorariums totaling $50,850.00
			Grants totaling $36,675.00
			Consulting, honorarium and miscellaneous payments totaling $416,717.82
			Miscellaneous payments totaling $100,000.00

Reviewer Comment: *Investigators with significant disclosable interests enrolled approximately 8.8% (N=46) of the total number of patients in Study 1023. Each individual investigator enrolled between 0.19-(b) (6)% of the population which is small and unlikely to individually affect the results of the study. Results of a sensitivity analyses performed by the FDA statistician excluding these sites are consistent with the primary efficacy endpoint results (results shown under Sensitivity Analyses).*

Patient Disposition

From September 26, 2013 to August 26, 2014, a total of 521 patients were randomized at 144 sites in 17 countries. An additional 16 sites received study drug but did not randomize any patients.

At the time of data cutoff on December 5, 2014, 107 (30.8%) in the palbociclib plus fulvestrant arm and 97 (55.7%) patients in the placebo plus fulvestrant arm had discontinued study treatment, while 238 (68.6%) patients in the palbociclib plus fulvestrant arm and 75 (43.1%) patients in the placebo plus fulvestrant arm were still on study treatment (as seen in Table 8).

Table 8. Study 1023 Patient Disposition

	Palbociclib plus Fulvestrant N (%)	Placebo plus Fulvestrant N (%)	Total N (%)
Randomized to study treatment	347	174	521
Randomized and not treated	2 (0.6)	2 (1.1)	4 (0.8)
Randomized and treated	345 (99.4)	172 (98.9)	517 (99.2)
Completed	0	0	0
Discontinued	107 (30.8)	97 (55.7)	204 (39.2)
Ongoing at data cutoff date	238 (68.6)	75 (43.1)	313 (60.1)
Reason for discontinuation			
AE (reason for palbociclib/placebo discontinuation)	9 (2.6)	3 (1.7)	12 (2.3)
AE (reason for fulvestrant discontinuation)	7 (2.0)	3 (1.7)	10 (1.9)
Global deterioration of health status	8 (2.3)	3 (1.7)	11 (2.1)
Lost to Follow-Up	0	0	0
Medication error without associated AE	0	0	0
Objective progression or relapse plus progressive disease	85 (24.5)	87 (50.0)	172 (33.0)
Protocol violation	0	0	0
Study terminated by the sponsor	0	0	0
Patient died	0	1 (0.6)	1 (0.2)
Patient refused to continue treatment for reason other than AE	1 (0.3)	1 (0.6)	2 (0.4)

Source: Modified from Study 1023 CSR Table 11 and Table 12; sbjdsp.xpt

Protocol Violations/Deviations

There were an equal number of protocol deviations reported in both treatment arms, with at least 1 protocol deviation reported in 69.5% of patients in each arm as seen in Table 9. Major protocol deviations occurred with respect to inclusion/exclusion criteria, study drug administration/study treatment, informed consent, disallowed medication, and SAE/AE.

Major protocol deviations were reported in a higher percentage of patients in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm. The difference was due to a higher percentage of patients in the palbociclib plus fulvestrant arm with major protocol deviations related to study drug administration/study treatment (21.0% vs 13.8%), and deviations related to informed consent (12.1% vs 5.7%).

All the protocol violations regarding SAE/AE in both arms were due to reporting not occurring within the required time frame. Proton pump inhibitors were the most common disallowed medication used by patients in both treatment arms. The most common inclusion/exclusion criteria protocol deviations included patients that had not come off of anti-cancer therapy at least two weeks prior to going on study. The majority of protocol deviations related to study drug administration/study treatment were due to patients that took palbociclib/placebo for 1-2 doses more than the scheduled 21 doses per cycle or palbociclib/placebo treatment not interrupted or reduced for toxicity as required by protocol. Informed consent document (ICD) deviations mainly included patients that did not have a properly signed ICD on file (missing time, all boxes not initialed, discordance in answers when different versions of consent signed), did not re-sign an ICD when updated versions became available or had vital signs/physical exam/labs performed prior to ICD being signed.

Table 9. Protocol Deviations in Study 1023

Protocol Deviation Category	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)
Any protocol deviation	241 (69.5)	121 (69.5)
AE/SAE	5 (1.4)	1 (0.6)
Disallowed medication	16 (4.6)	11 (6.3)
Inclusion/exclusion criteria	20 (5.8)	13 (7.5)
Informed consent	42 (12.1)	10 (5.7)
Study drug administration/study treatment	73 (21.1)	24 (13.8)
Other	15 (4.3)	9 (5.2)
Procedures/tests	192 (55.3)	92 (52.9)
Visit schedule	53 (15.3)	31 (17.8)
Any major protocol deviation	125 (36.0)	51 (29.3)
AE/SAE	5 (1.4)	1 (0.6)
Disallowed medication	16 (4.6)	11 (6.3)
Inclusion/exclusion criteria	20 (5.8)	13 (7.5)
Informed consent	42 (12.1)	10 (5.7)
Study drug administration/study treatment	73 (21.0)	24 (13.8)

Source: Modified from Study 1023 CSR Table 13; Table 16.2.2.2

Reviewer Comment: *All protocol deviations were reviewed. The nature of these deviations should not have affected the efficacy results. In addition, results for Sensitivity Analysis #5*

(influence of deviations in tumor lesion assessment) support the primary efficacy endpoint results.

Enrollment by Country:
Breakdown of enrollment by country is shown in Table 10.

Table 10. Study Enrollment by Country

Country	Palbociclib plus Fulvestrant N=347 n (%)	Placebo plus Fulvestrant N=174 n (%)
United States	129 (37)	72 (41)
Ukraine	32 (9)	12 (7)
Korea	24 (7)	19 (11)
Canada	29 (8)	10 (6)
Italy	18 (5)	18 (10)
Japan	27 (8)	8 (5)
Australia	23 (7)	9 (5)
Belgium	20 (6)	7 (4)
Russia	14 (4)	3 (2)
United Kingdom	9 (3)	4 (2)
Netherlands	6 (2)	3 (2)
Romania	4 (1)	4 (2)
Portugal	2 (<1)	4 (2)
Taiwan	4 (1)	0
Germany	2 (<1)	1 (1)
Ireland	3 (1)	0
Turkey	1 (<1)	0

Source: demog.xpt

Reviewer Comment: *This was an international study with patients enrolled from 17 countries. The top five countries for enrollment were the United States, Ukraine, Korea, Canada and Italy, with a 39% of patients enrolled from the United States.*

Table 11. Demographic Characteristics for Study 1023

Demographic Parameters	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Sex			
Male	0	0	0
Female	347 (100)	174 (100)	521 (100)
Age			
Mean years (SD)	56.9 (11.7)	56.8 (10.4)	56.9 (11.3)
Median (years)	57	56	57
Min, max (years)	30-88	29-80	29-88
Age Group			
≥ 17 - < 65 years	261 (75.2)	131 (75.3)	392(75.2)
≥ 65 - < 75 years	59 (17.0)	37 (21.3)	96 (18.4)
≥ 75 years	27 (7.8)	6 (3.4)	33 (6.3)
Race			
White	252 (72.6)	133 (76.4)	385 (73.9)
Black or African American	12 (3.5)	8 (4.6)	20 (3.8)
Asian	74 (21.3)	31 (17.8)	105 (20.2)
Other	8 (2.3)	1 (0.6)	9 (1.7)
Ethnicity			
Hispanic or Latino	17 (4.9)	11 (6.3)	28 (5.4)
Not Hispanic or Latino	329 (94.8)	161 (92.5)	490 (94)

Source: Modified from Study 1023 CSR Table 15 and demog.xpt

Reviewer Comment: *Baseline patient demographics were well balanced between the two arms. All patients were female and a majority of patients were of White Race. Unfortunately, as with most clinical trials, there was an underrepresentation of Black patients and Hispanic/Latino patients.*

Table 12. Baseline Disease Characteristics for Study 1023

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Measurable disease			
Yes	268 (77.2)	138 (79.3)	406 (77.9)
No	79 (22.8)	36 (20.7)	115 (22.1)
Adequate baseline assessment			
Yes	346 (99.7)	174 (100)	520 (99.8)
No	1 (0.3)	0	1 (0.2)
Bone Only Disease			
Yes	84 (24.2)	37 (21.2)	121 (23.2)
ER Status			
Positive	339 (97.7)	167 (96.0)	506 (97.1)
Negative	1 (0.3)	2 (1.1)	3 (0.6)
Missing	7 (2.0)	5 (2.9)	12 (2.3)
PR Status			
Positive	243 (70.0)	117 (67.2)	360 (69.1)
Negative	91 (26.2)	48 (27.6)	139 (26.7)
Missing	13 (3.7)	9 (5.2)	22 (4.2)
HER2 status			
Positive	2 (0.6)	2 (1.1)	4 (0.8)
Negative	341 (98.3)	171 (98.3)	512 (98.3)
Equivocal	3 (0.9)	1 (0.6)	4 (0.8)
Missing	1 (0.3)	0	1 (0.2)
Histopathologic classification			
Ductal	233 (67.1)	106 (60.9)	339 (65.1)
Lobular	40 (11.5)	22 (12.6)	62 (11.9)
Other	74 (21.3)	46 (26.4)	120 (23.0)
Histologic Grade			
1	22 (6.3)	16 (9.2)	38 (7.3)
2	162 (46.7)	79 (45.4)	241 (46.3)
3	93 (26.8)	40 (23.0)	133 (25.5)
Stage at Initial Diagnosis			
I	26 (7.5)	13 (7.5)	39 (7.5)
II	120 (34.6)	56 (32.2)	176 (33.8)

III	69 (19.9)	47 (27.0)	116 (22.3)
IV	86 (24.8)	36 (20.7)	122 (23.4)
Other/Unknown	46 (13.3)	22 (12.6)	68 (13.1)
ECOG Performance Status			
0	207 (59.7)	115 (66.1)	322 (61.8)
1	140 (40.3)	59 (33.9)	199 (38.2)
Involved Disease Sites			
Bone	163 (75.8)	129 (74.1)	392 (75.2)
Breast	61 (17.6)	19 (10.9)	80 (15.4)
Liver	127 (36.6)	81 (46.6)	208 (39.9)
Lung	103 (29.7)	44 (25.3)	147 (28.2)
Lymph Node	138 (39.8)	63 (36.2)	201 (38.6)
Other	109 (31.4)	46 (26.4)	155 (29.8)

Source: Modified from Study 1023 CSR Table 16 demog.xpt, and othbas.xpt

Reviewer Comment: *There was a difference (≥5%) in baseline characteristics between treatment arms regarding ECOG performance status, histologic classification, stage at initial diagnosis and involved sites of disease. These differences are unlikely to have affected the efficacy results.*

Stratification Factors:
Patients were stratified by documented sensitivity to prior hormonal therapy (yes vs. no), by menopausal status at study entry (pre-/peri- vs. post-menopausal), and by the presence of visceral metastases (yes vs. no). Sensitivity to prior hormonal therapy was defined as either: 1) documented clinical benefit (complete response, partial response, stable disease ≥24 weeks) to at least 1 prior hormonal therapy in the metastatic setting, OR 2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Postmenopausal status was defined by at least one of the following criteria: age>60 years; age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and serum estradiol and FSH level within the laboratory's reference range for postmenopausal females; documented bilateral oophorectomy; medically confirmed ovarian failure. Visceral metastases refer to lung, liver, brain, pleural, and peritoneal involvement. Stratification factors are well balanced between arms as seen in Table 13.

Table 13. Stratification Factors for Study 1023

	Palbociclib plus Fulvestrant N=347 N (%)	Placebo plus Fulvestrant N=174 N (%)	Total N=521 N (%)
Based on randomization:			
Visceral metastases			
Yes	206 (59.4)	105 (60.3)	311 (59.7)
No	141 (40.6)	69 (39.7)	210 (40.3)
Documented sensitivity to prior hormonal therapy			
Yes	274 (79.0)	136 (78.2)	410 (78.7)
No	73 (21.0)	38 (21.8)	111 (21.3)
Menopausal status			
Pre-/perimenopausal	72 (20.7)	36 (20.7)	108 (20.7)
Postmenopausal	275 (79.3)	138 (79.2)	413 (79.3)
Based on CRF:			
Visceral metastases			
Yes	206 (59.4)	105 (60.3)	311 (59.7)
No	141 (40.6)	69 (39.7)	210 (40.3)
Documented sensitivity to prior hormonal therapy			
Yes	273 (78.7)	133 (76.4)	406 (77.9)
No	74 (21.3)	41 (23.6)	115 (22.1)
Menopausal status			
Pre-/perimenopausal	71 (20.5)	36 (20.7)	107 (20.5)
Postmenopausal	276 (79.5)	138 (79.3)	414 (79.5)

Source: Study 1023 CSR Table 17

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

- **Concomitant Medications**
  Almost all patients in both treatment arms received concomitant drug treatment during the study (95.9% of patients in the palbociclib plus fulvestrant arm and 96.5% of patients in the placebo plus fulvestrant arm).

  The top 5 most commonly used concomitant drug treatment for patients in the palbociclib plus fulvestrant arm vs patients in the placebo plus fulvestrant arm, respectively are as follows: paracetamol (24.6% vs 26.2%), denosumab (21.7% vs 20.3%), goserelin (20.0% vs 20.3%), zoledronic acid (18.3% vs 21.5% of patients) and ergocalciferol (16.8% vs 12.2%). The use of goserelin in approximately 20% of each treatment arm correlates to the 20% peri/premenopausal population in each treatment

arm. Overall, approximately half the patients in each treatment arm were on treatment for bone disease as seen in Table 14.

Table 14. Concomitant Use of Treatment for Bone Disease in Study 1023

	Palbociclib plus Fulvestrant N=345 N (%)	Placebo plus Fulvestrant N=173 N (%)
Drugs for Treatment of Bone Disease	173 (50.1)	83 (47.1)
Actonel combination	0	1 (0.6)
Alendronate sodium	4 (1.2)	1 (0.6)
Clodronic acid	6 (1.7)	0
Denosumab	75 (21.7)	35 (20.3)
Ibandronate sodium	6 (1.7)	1 (0.6)
Ibadronic acid	4 (1.2)	0
Pamidronate disodium	19 (5.5)	8 (4.7)
Pamidronic acid	1 (0.3)	0
Zolendronic acid	63 (18.3)	37 (21.5)

Source: Modified from Study 1023 CSR Table 14.4.2.5

- **Subsequent systemic therapies**
  As of the December 2014 data cutoff date, 19.6% and 40.8% of patients in the palbociclib plus fulvestrant arm and in the placebo plus fulvestrant arm respectively, had started a new anti-cancer therapy. The anti-cancer therapies most commonly administered were capecitabine (8.4% vs 12.1%), paclitaxel (4.6% vs 10.9%), exemestane (3.5% vs 8.0%), and everolimus (3.2% and 8.6%).

Efficacy Results – Primary Endpoint

The primary endpoint for Study 1023 was investigator-assessed PFS. A planned interim analysis of the primary PFS endpoint was to be performed after at least 143 investigator-assessed PFS events (approximately 60% of the total PFS events expected at the time of final analysis). Due to a high accrual rate in Study 1023 and the operational logistics of cleaning the data for the interim analysis, a total of 195 events (82% of the total planned final PFS events expected) were included in the interim analysis.

As of the December 5, 2014 data cutoff for the interim analysis, 195 investigator-assessed PFS events had occurred, 102 (29.4%) patients in the palbociclib plus fulvestrant arm and 93 (53.4%) in the placebo plus fulvestrant arm. At the time of the interim analysis, the median PFS

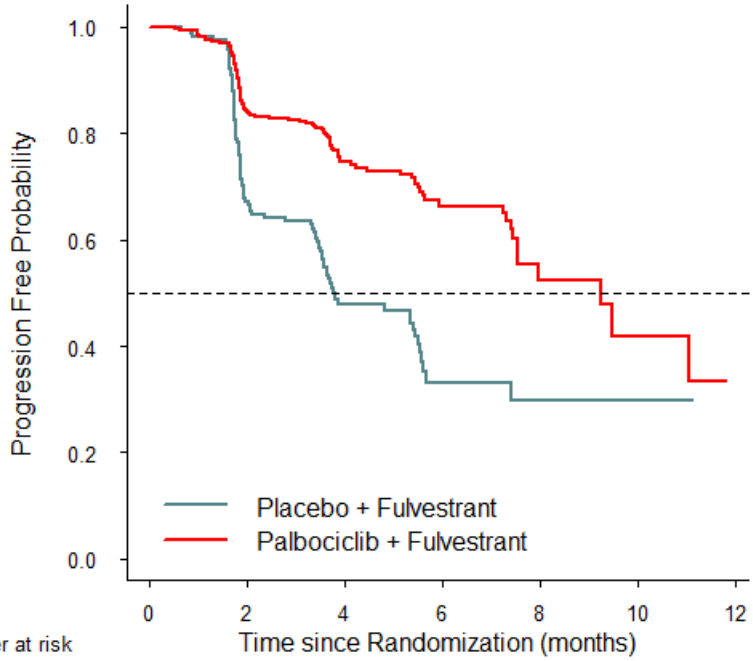
in the palbociclib plus fulvestrant arm was 9.2 months compared to 3.8 months for 174 patients randomized to placebo plus fulvestrant arm (HR=0.42; 95% CI: 0.32, 0.56; p<0.000001), as summarized in Table 15 and Figure 2.

Table 15. Primary endpoint: Investigator-Assessed PFS (December 5, 2014 cut-off)

	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	101 (29.1)	92 (52.9)
Censored (%)	246 (70.9)	82 (47.1)
Median PFS (months) 95% CI	9.2 (7.5, NR)	3.8 (3.5, 5.5)
Hazard Ratio (stratified)* 95% confidence interval	0.42 (0.32, 0.56)	
p-value	<0.0001	

Source: FDA Statistician
**stratified by documented sensitivity to prior hormonal therapy, menopausal status, and by the presence of visceral metastases; NR=not reached*

Figure 2. KM Curve for Investigator-Assessed PFS (December 5, 2014 cut-off)



Source: FDA Statistician

Reviewer Comment: *A clinically meaningful and statistically significant 5.4 months improvement in the primary endpoint of investigator-assessed PFS was seen in the palbociclib treatment arm at the time of interim analysis. The study was stopped for efficacy at the time of the interim analysis.*

Of note, the control arm of (placebo plus fulvestrant) did not perform as well as expected with a median PFS of only 3.8 months compared to a predicted 6.0 months. This difference may be due to the fact that Study 1023 allowed enrollment of peri/premenopausal patients and patients with >1 prior therapy for advanced/metastatic breast cancer. Both of these patient populations were not eligible for the phase 2 study (9) in which the statistical assumptions were based on for Study 1023 and may have conferred a worse prognosis resulting in shorter median PFS.

Sensitivity Analyses:
The applicant performed eight sensitivity analyses for PFS to evaluate the impact of

stratification factors and analysis populations, results are shown in Table 16. Briefly, the sensitivity analyses performed were as follows:

- Sensitivity analysis 1: Influence of analysis population; based on As Treated (AT) population
- Sensitivity analysis 2: A 1-sided unstratified log-rank test was used to compare treatments and the HR was based on an unstratified Cox proportional hazards model.
- Sensitivity analysis 3: To investigate whether the stratification factors and important covariates influenced the outcome of the primary endpoint PFS.
- Sensitivity analysis 4: Influence of disease assessment scheduling. If disease progression was documented between 2 scheduled tumor assessments, then the date of progression was assigned to the earlier scheduled tumor assessment. In the event of death, the date of the endpoint was not adjusted.
- Sensitivity analysis 5: Influence of deviations in tumor lesion assessment.
- Sensitivity analysis 6.1: Influence of bone-only disease patients. Patients with bone-only disease with fracture, radiation therapy, surgery, ECOG at least 2 point increase from baseline or change of therapy were censored at the date of prior tumor assessment with no PD.
- Sensitivity analysis 6.2: Influence of bone-only disease patients: Patients with bone-only disease with fracture, radiation therapy, surgery, ECOG at least 2 point increase from baseline or change of therapy were considered as events.
- Sensitivity analysis 6.3: Influence of bone-only disease patients: Bone-only disease patients were excluded from the analysis.
- Sensitivity analysis 7: Influence of Missing Data: The following missing PFS data that might have resulted in the censored PFS data in the primary analysis were considered PFS events in addition to the documented PD and death: new anti-cancer treatment, lost to follow-up, consent withdrawal, medication error without associated AE.
- Sensitivity analysis 8: Influence of potential investigator bias. Random sample BICR data and investigator assessed PFS (event) data were combined. For events identified by both BICR and investigator, BICR data were used to determine event time. For patients who were censored by both BICR and investigator, BICR (when applicable) data were used to determine the censoring time.

Table 16. PFS Sensitivity Analyses

Sensitivity analysis	HR (95% CI)	p-value	Palbociclib plus fulvestrant events	Placebo plus fulvestrant events
1	0.422 (0.318, 0.560)	<0.000001	102	93
2	0.417 (0.314, 0.553)	<0.000001	102	93
3	0.395 (0.297, 0.525)	<0.000001	102	93
4	0.426 (0.321, 0.565)	<0.000001	102	93
5	0.422 (0.318, 0.560)103	<0.000001	102	93
6.1	0.422 (0.318, 0.560)	<0.000001	102	93
6.2	0.432 (0.326, 0.573)	<0.000001	104	93
6.3	0.411 (0.300, 0.563)	<0.000001	83	77
7	0.438 (0.335, 0.574)	<0.000001	114	101
8	0.378 (0.287, 0.498)	<0.000001	103	103

CI=confidence interval; for sensitivity analyses 1 and 4 to 8, stratified hazard ratios are presented, for sensitivity analyses 2 and 3 unstratified hazard ratios; 1-sided p-values are reported except for sensitivity analysis 3 (2-sided p-value)
Source: Modified from Study 1023 CSR Table 20 modified

The FDA statistician performed an additional sensitivity analyses on PFS assessing the impact of sites with investigators that had financial disclosures.

FDA Sensitivity Analysis: Sites with investigators with financial disclosures were omitted. The results were consistent with the primary findings, with a 5.5 month improvement in PFS (9.2 vs 3.7 months) and a stratified HR = 0.39 (95% CI = 0.293, 0.532).

Reviewer Comment: *The planned sensitivity analyses results are all consistent with the primary efficacy endpoint results. The additional FDA sensitivity analysis also supports the primary efficacy endpoint results.*

Table 17. Censored Patients in Study 1023

	Palbociclib plus fulvestrant N=347 N (%)	Placebo plus fulvestrant N=174 N (%)
Number Censored	245 (70.1)	81 (55.1)
Reason for censorship:		
No adequate baseline assessments	1 (<1)	0
No on-study disease assessments	7 (2.0)	7 (4.0)
Given new anti-cancer treatment prior to disease progression and after last dose of study treatment	8 (2.3)	4 (2.3)
Discontinued study without disease progression or death: Withdrew consent for follow-up Other	 1 (<1) 1 (<1)	 0 0
In follow-up for progression	227 (65.4)	70 (40.2)

Source: Modified from Study 1023 CSR Table 19

Reviewer Comment: *Reasons for censoring were appropriate in the two treatment arms of this double-blinded, placebo control study.*

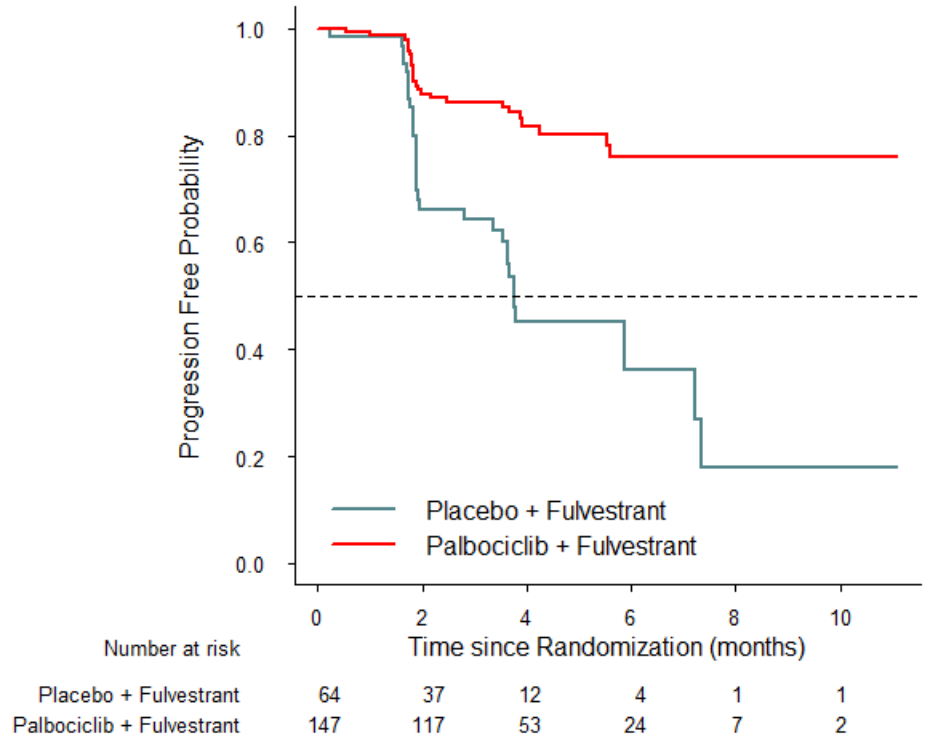
PFS Based on Blinded Independent Central Review (BICR):
A protocol prespecified BICR was conducted by (b) (4) on approximately 40% of the total population to corroborate the investigator-assessed PFS results. A stratified simple random sampling approach was utilized to randomly select patients from each stratum based on the blinded enrollment data. The BICR audit was not intended to provide an alternative means of definitive analysis.

The investigators were not aware, which patients were randomly selected for the BICR review. The independent third-party core imaging laboratory assessed tumor progression based on the review of scans, physical examination data and other data, from the final data cut for this randomly selected subgroup of the study population. The following materials were forwarded for independent review:

- All imaging studies performed on study
- Photographs of sites of disease assessed using clinical methods. Details concerning clinically assessed lesions were collected on the CRFs and made available to the independent core imaging laboratory.

Results for the BICR are seen below in Figure 3.

Figure 3. PFS Results for BICR Audit in Study 1023



Source: FDA Statistician

Reviewer Comment: *In the pivotal study used for the basis of accelerated approval of palbociclib {Study 1003, PALOMA-1 (Part 1)}, there were censoring differences between the investigator and BICR that led to discordant results between the BICR assessed PFS and investigator assessed PFS. Although, Study 1023 did not have a full BICR assessment, no discordance was observed between the BICR audit results and investigator assessed PFS. Based on three different methods (NCI method, Pharma method and a multiple imputation approach developed internally at the FDA), results of the BICR audit support the primary analysis using investigator-assessed PFS. For further details regarding results from the different methods, refer to the Statistical Review by Dr. Erik Bloomquist for the palbociclib sNDA.*

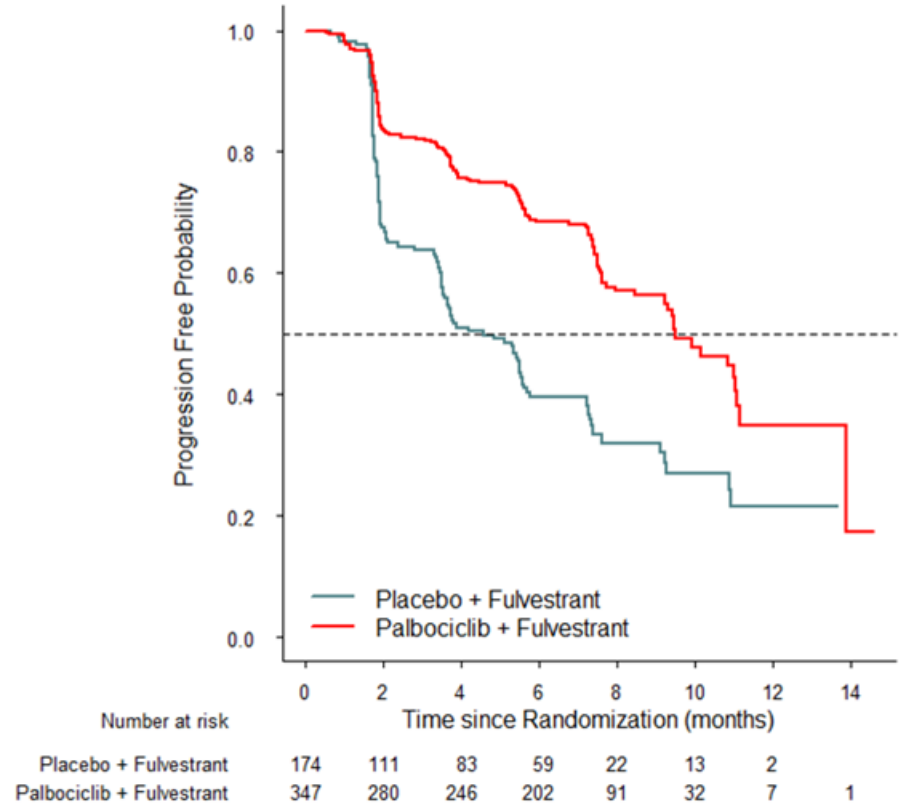
Updated Progression-Free Survival Analysis:
At the recommendation of the European Union (EU) Rapporteurs, the Applicant performed an exploratory updated analysis of PFS. The updated analysis was based on a March 16, 2015 data cut-off date and 259 PFS events (Table 18 and Figure 4).

Table 18. Investigator-Assessed PFS (March 16, 2015 cut-off)

	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	145	113
Censored (%)	202	61
Median PFS (months) 95% CI	9.5 (9.2, 11.0)	4.6 (3.5, 5.6)
Hazard Ratio (stratified)* 95% confidence interval	0.46 (0.36, 0.59)	
p-value	<0.0001	

Source: FDA Statistician
**stratified by documented sensitivity to prior hormonal therapy, menopausal status, and by the presence of visceral metastases*

Figure 4. KM Curve for Investigator-Assessed PFS (March 16, 2015 cut-off)



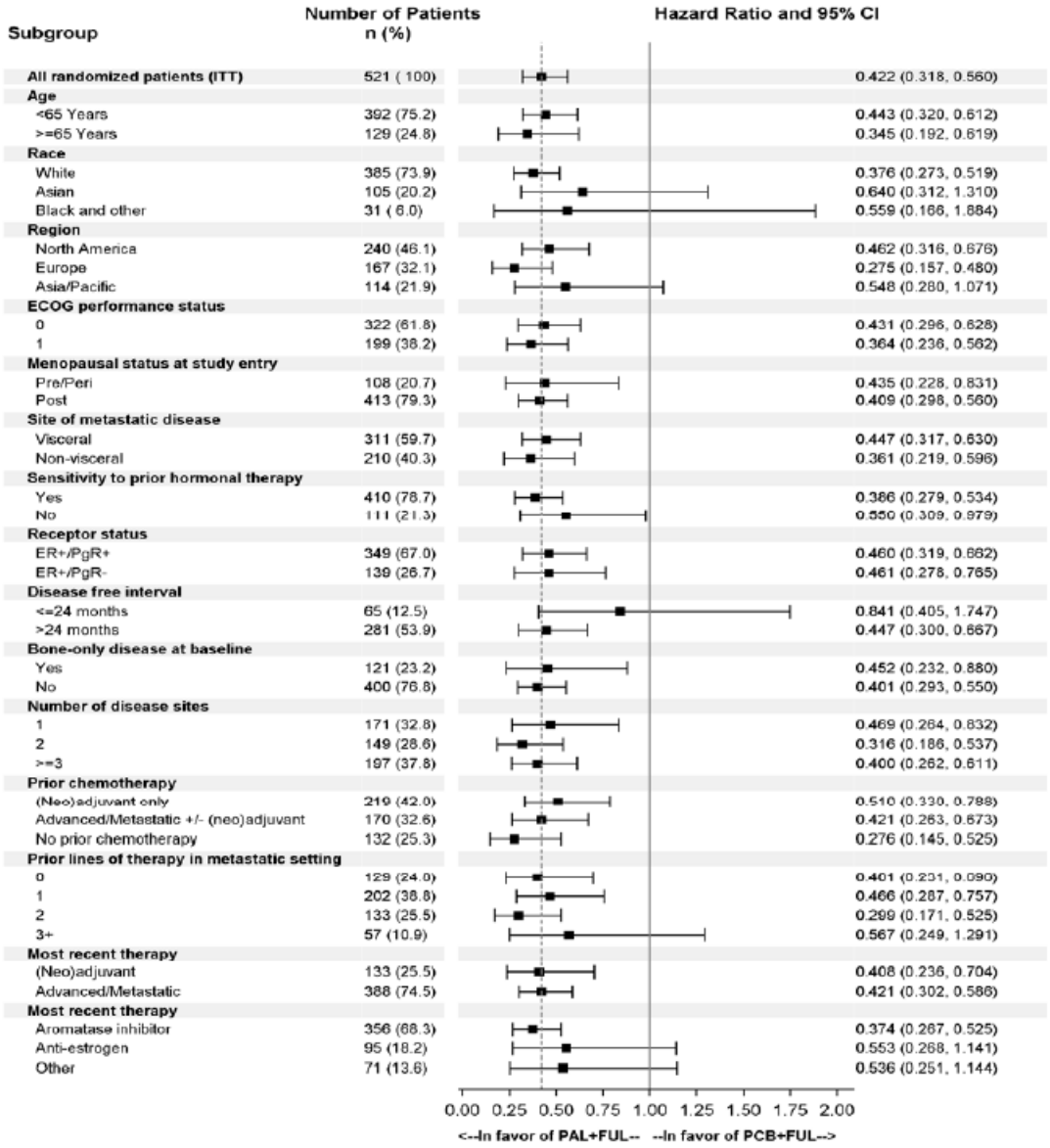
Source: FDA Statistician

Reviewer Comment: *The updated results support the results from the interim analysis for the primary efficacy endpoint. The DMC meeting for the interim analysis occurred on April 7, 2015. The DMC recommendation to stop the study early due to efficacy results was communicated to Pfizer on April 7, 2015 and the data were presented publically for the first time at ASCO on June 1, 2015. There should have been no impact of the released interim data on the updated analysis since the data cut-off (March 16, 2015) for the updated analysis was three weeks prior to the DMC meeting.*

Although exploratory, the review team chose to include the updated results in the label since they were more mature, with narrower confidence intervals, providing a better estimate regarding the efficacy of palbociclib plus fulvestrant.

Subgroup Analyses:
Several subgroups of various demographic and baseline characteristics were examined by the Applicant. The forest plots of these subgroups analyses of PFS are shown in Figure 5.

Figure 5. Forest Plot of Progression-Free Survival by Additional Baseline Characteristics, Investigator Assessment – Intent-to-Treat Population (Applicant Figure)



Source: Study 1023 CSR Figure 2

Reviewer Comment: *The treatment effect is consistent in the different subgroups. In some cases, such as race, disease-free interval (≤24 months), prior lines of therapy (+3) and most recent therapy (anti-estrogen and other), the spread of the confidence intervals is broad due to a small number of patients. No subgroup demonstrates a detriment with palbociclib plus fulvestrant treatment.*

Data Quality and Integrity – Reviewers' Assessment

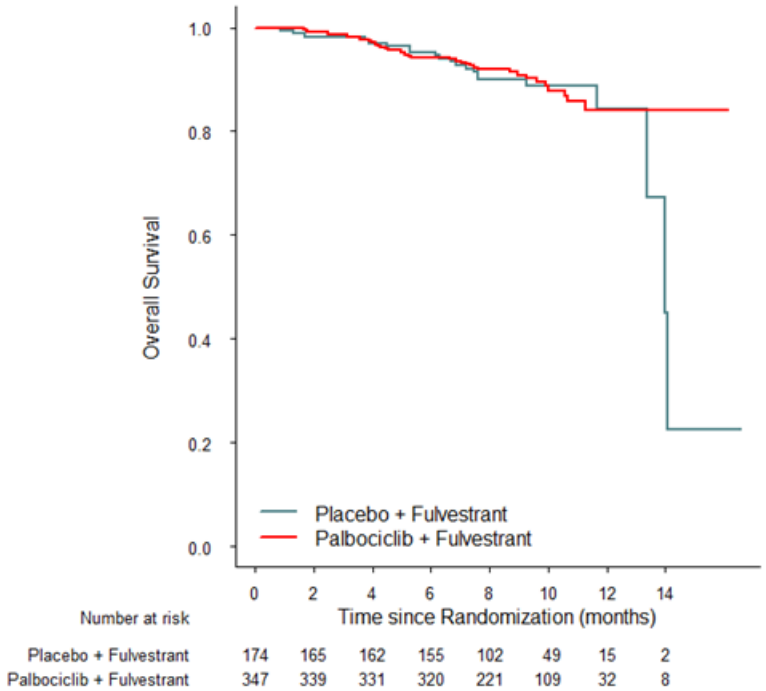
The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the Applicant throughout the review process were addressed in a timely fashion.

Efficacy Results – Secondary and other relevant endpoints

Key secondary endpoints included overall survival, objective response rate, clinical benefit rate, and duration of response.

Overall Survival:
At the data cut-off of March 16, 2015, there were 57 deaths among the 521 patients. The OS data was immature with only 29% of the planned 198 events. OS results are shown below in Figure 6.

Figure 6. Overall Survival in Study 1023



Source: FDA Statistician

Objective Response Rate (ORR):

At the March 2015 cut-off, as per investigator-assessment, ORR was 24.6% in the palbociclib plus fulvestrant arm compared with 10.9% in the placebo plus fulvestrant arm for patients with measurable disease at baseline. Results at the time of interim analysis and final analysis are shown in Table 19.

Clinical Benefit Response (CBR):

CBR was defined as CR or PR or SD ≥24 weeks according to the RECIST version 1.1. At the March 2015 cut-off, for patients with baseline measurable disease, the CBR rates were 66.6% in the palbociclib plus fulvestrant arm and 39.7% in the placebo plus fulvestrant arm. Results at the time of interim analysis and final analysis are shown in Table 19.

Duration of Response (DOR):

DOR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. At the March 2015 cut-off, DOR was 9.3 months in the palbociclib plus fulvestrant arm and 7.6 months in the placebo plus fulvestrant arm. Results at the time of interim analysis and final analysis are shown in Table 19.

Table 19. Secondary Endpoint Results for Study 1023

	Interim Analysis (December 5, 2014 Cutoff)		**Updated/Final Analysis (March 16, 2015 Cutoff)**	
	Palbociclib plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**	**Palbociclib plus Fulvestrant (N=347)**	**Placebo plus Fulvestrant (N=174)**
ORR	10.4%	6.3%	19.0%	8.6%
ORR (measurable disease)	13.4%	8.0%	24.6%	10.9%
CBR	34.0%	19.0%	66.6%	39.7%
DOR (months)	9.3	5.7	9.3	7.6

N=number of patients; PFS=progression-free survival; CI=confidence interval; NE=not estimable; ORR=objective response rate; CBR=clinical benefit response; DOR=duration of response.

Reviewer comment: *The OS results were immature at the time of analysis. Numerically, results for ORR, CBR and DOR support the primary efficacy endpoint results.*

Palbociclib has limited single agent activity, with a clinically meaningful benefit seen only when given in combination with endocrine therapies such as letrozole or fulvestrant. None of the patients in a phase 1 dose-escalation study conducted with palbociclib in patients with retinoblastoma protein (Rb)-positive advanced solid tumors had a PR or CR as per RECIST criteria. 13 patients (35%) maintained stable disease (SD) for at least 2 cycles.(2)SD was observed in the following tumor types: liposarcoma (3 patients), testicular (2 patients), and kidney, ovarian, breast, appendiceal, peritoneal, melanoma, thymoma, and lung (1 patient each). SD lasted ≥4 cycles in 10 patients (27.0%) and ≥10 cycles in 6 patients (16.2%). (11) A subsequent phase 2 study using single agent palbociclib in patients with Rb-positive advanced breast cancer resulted in an ORR of 5% in all patients (n=37) and 6% in patients with HR-positive disease (n=33). No patients had a CR per RECIST criteria. Clinical benefit rate (defined as patients with PR and patients with >6 month SD) was 19% in the total population and 21% in patients with HR-positive disease. Median PFS overall was 3.7 months [95% confidence interval (CI), 1.9–5.1]. (4)

Fulvestrant does have known single agent activity and has been approved as monotherapy in the US since 2002 for the treatment of postmenopausal women with HR-positive metastatic breast cancer whose disease has progressed following antiestrogen therapy (1). However, as seen with the results from Study 1023, the addition of palbociclib to fulvestrant therapy further improves upon the benefit derived from fulvestrant therapy alone.

Dose/Dose Response

Not applicable.

Durability of Response

These issues are addressed throughout the efficacy review given that the primary endpoint (PFS) of the trial is a time to event endpoint.

Persistence of Effect

These issues are addressed throughout the efficacy review given that the primary endpoint of the trial is a time to event endpoint. The duration of response for the ORR also supports the primary endpoint results.

Additional Analyses Conducted on the Individual Trial

None

7 Integrated Review of Effectiveness

7.1. Integrated Assessment of Effectiveness

HR-positive/HER2-negative advanced or metastatic breast cancer is a life-threatening disease that clearly has unmet medical needs in its treatment. Although there are several endocrine and chemotherapy agents available to these patients; resistance often develops, leading to progression of disease and ultimately death.

In this sNDA, the Applicant relied on results from a single study, Study 1023. Study 1023 was a randomized, double-blind, placebo- controlled study in women with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed after prior endocrine therapy. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator assessed PFS. At the final analysis, the median PFS in the palbociclib plus fulvestrant arm was 9.5 months compared to 4.6 months in the placebo plus fulvestrant arm (HR=0.46; 95% CI: 0.36, 0.59; p<0.000001). Palbociclib plus fulvestrant showed a 4.9 month improvement in median PFS compared to placebo plus fulvestrant which is both clinically meaningful and statistically significant. Results of a BICR audit, subgroup analyses and sensitivity analyses all support the primary efficacy endpoint results. OS results are immature at this time. In conclusion, based on a favorable risk-benefit profile for palbociclib in combination with fulvestrant, the reviewers recommend regular approval for the following indication "FASLODEX is an estrogen receptor antagonist indicated in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer whose disease progressed after endocrine therapy.

8 Review of Safety

8.1. Safety Review Approach

In this sNDA for fulvestrant, the Applicant cross references safety data from Study 1023, a Phase 3 trial of palbociclib plus fulvestrant versus fulvestrant and placebo that was submitted with the sNDA for palbociclib. A total of 345 patients received fulvestrant plus palbociclib in

Study 1023 (347 patients randomized). Adverse events were assessed during the treatment period and for 28 days after the last dose of study drug. Laboratories were collected at baseline and every 15 days during the first 2 cycles, followed by every 28 days starting at day 1 of cycle 3. Hematology labs included hemoglobin, WBC, absolute neutrophil count, platelet count. Blood chemistries included AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN), serum creatinine, and albumin. Upon approval of Amendment 2, hemoglobin A1c was measured every 3 months to characterize whether or not palbociclib affects glucose metabolism. There were no clinical holds for safety during the development of palbociclib.

The 90-Day Safety Update provided cumulative safety information as of July 31st, 2015 for Study 1023.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The duration of exposure to palbociclib, placebo or fulvestrant in Study 1023 is summarized in Table 10 below. As of July 31, 2015, 39.2% of patient in the palbociclib plus fulvestrant arm and 19.5% of patients in the placebo plus fulvestrant arm were still receiving protocol directed therapy. Dose reductions were not allowed for fulvestrant. The median duration of palbociclib and fulvestrant exposure in the palbociclib plus fulvestrant arm was approximately 11 months. The median daily dose of palbociclib was 125.0 mg (range 81-131 mg).

Table 20. Summary of Patient Exposure to Palbociclib, Placebo, and Fulvestrant in Study 1023

	Palbociclib plus Fulvestrant (n= 345)		**Placebo plus Fulvestrant (n=172)**	
	Palbociclib	Fulvestrant	Placebo	Fulvestrant
Median number of cycles (range)	12 (1-21)	12 (1-21)	5 (1-22)	5 (1-22)
Median treatment duration in days (range)	330 (1-596)	341 (28-596)	137 (14-611)	145 (27-618)
Patients with at least 1 dose reduction (%)	128 (37.1)	NA[1]	3 (1.7)	NA
Patients with 2 dose reductions (%)	18 (5.2)	NA	0	NA
Patients with at least 1 dose interruption (%)	286 (82.9)	11 (3.2)	104 (60.5)	2 (1.2)
Patients with cycle delay (%)[2]	187 (54,2)	--	22 (12.8)	--
Mean cumulative dose	22,514 (13,237)	5,502 (2,722)	17,829 (13,723)	4,064 (2,712)

in mg (SD)				
Median cumulative dose in mg (range)	24,175 (125-54,500)	6,500 (500-11,500)	12,750 (1,750-57,625)	3,000 (500-11,500)
Mean relative dose intensity (SD)[3]	85.6 (15.4)	96.3 (6.8)	97.7 (4.9)	98.9 (5.7)
Median relative dose intensity (range)	89.8 (22-107)	98.4 (50-106)	99.5 (69-108)	100 (50-108)

[1] Protocol did not allow for the fulvestrant dose to be reduced, but a single dose could be skipped or dosing delayed because of fulvestrant related toxicity.
[2] Cycle delay defined as a 2-day or longer delay in the cycle start date (Cycles 1 and 2) or a 7-day or longer delay in Cycles 3 and beyond.
[3] Relative dose intensity = (actual dose intensity/intended dose intensity)*100%
Source: 90-Day Safety Update, Tables 4 and 5, page 32-33

8.2.2. Relevant characteristics of the safety population:

Demographic information for the 517 patients in Study 1023 is included in Section 6.1.2 above. In summary, the two treatment arms were well balanced in terms of baseline characteristics. All patients in this study were women whose median age was 57 (30-88) years in the palbociclib plus fulvestrant arm and 56 (29-80) years in the placebo plus fulvestrant arm. Most patients in either treatment arm were White (72.6% in the palbociclib plus fulvestrant arm and 76.4% in the placebo plus fulvestrant arm). The two treatment arms were well balanced in terms of ECOG PS at baseline. More than half of the patients in either treatment arm had an ECOG PS of 0 at baseline. Prior treatments for patients in this study were also generally well balanced between the two treatment arms. The majority of patients in either arm had undergone prior surgery (82% in the palbociclib plus fulvestrant arm and 85% in the placebo plus fulvestrant arm); most patients in each treatment arm had received prior radiotherapy (68% and 75%, respectively); and all patients in either treatment arm had received prior systemic therapy.

8.2.3. Adequacy of the safety database:

The safety database from Study 1023 is adequate. The age and sex of the patients is as expected for patients with breast cancer. Of note, there were no males included in Study 1023. Minorities are also underrepresented in this trial. The performance status of the patients entered on this trial is greater than the performance status of patients with breast cancer as a whole.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall, data quality for this study was generally acceptable. Case report forms (CRFs) were reviewed and compared to the datasets and the patient narratives. There were some inconsistencies between the AE dataset and CRFs, as further described in this review.

8.3.2. Categorization of Adverse Events

The applicant defined an adverse event as any untoward medical occurrence in a clinical investigation patient administered a product or medical device, with or without a causal relationship with the treatment or usage. An abnormal objective test finding was reported as an AE if the test result was associated with accompanying symptoms, and/or required additional diagnostic testing or medical/surgical intervention, and/or led to a change in dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy, and/or was considered to be an AE by the investigator or the Applicant.

Reviewer Comment: *The definition of AE led to under reporting of many abnormal laboratory findings and possibly other types of abnormal subjective and objective findings in the patients.*

An SAE was defined as any untoward medical occurrence at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in congenital anomaly/birth defect. All AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 and AEs were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 criteria. AEs were summarized by MedDRA primary system organ class (SOC), and by Preferred term (PT). Treatment emergent adverse events were defined as events reported up to 30 days after the last dose of study medication.

8.3.3. Routine Clinical Tests

In Study 1023, routine laboratory tests including a CBC with differential (hemoglobin, WBC, absolute neutrophil count, lymphocytes, and platelet count) and chemistry (AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN), serum creatinine, and albumin) were collected at baseline and at each cycle. During the first two cycles, laboratories were checked every 2 weeks. Upon approval of Amendment 1, patients underwent an ophthalmologic exam by an ophthalmologist at screening, during study treatment on Cycle 4 Day 1, on Cycle 7 Day 1, on Cycle 13 Day 1, every 12 months thereafter, and at the End of Treatment/Withdrawal Visit. Upon approval of Amendment 2, hemoglobin A1c was measured every 3 months from the date of randomization. Ocular safety assessments included the Snellen best corrected visual acuity and refraction tests, intraocular pressure measurement, slit-lamp biomicroscopy, lens grading, and ophthalmoscopy. A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure, and pulse rate were carried out at Screening, Day 1 of every cycle, and at the End of Treatment/Withdrawal visit. A 12-Lead EKG was performed (in triplicate) at screening and also at the End of Treatment/Withdrawal Visit.

8.4. Safety Results

Deaths

Deaths in Study 1023: As of July 31st, 2015, four of 345 patients (1.2%) in the palbociclib plus fulvestrant arm and three of 172 patients (1.7%) in the placebo plus fulvestrant arm died on-study within 28 days of the last dose of palbociclib/placebo. The majority of deaths on both arms were due to disease progression. Per investigator assessment, no deaths were reported due to toxicity of palbociclib or fulvestrant. A review of the narratives of the seven patients was performed. Four patients died due to progressive disease, one patient in the palbociclib plus fulvestrant arm died from DIC presumably related to underlying malignancy or sepsis, one patient in the palbociclib plus fulvestrant arm died of neutropenic sepsis 22 days after receiving study drug, and one patient in the placebo plus fulvestrant arm died of intracerebral hemorrhage presumably related to underlying AVM or asymptomatic single CNS metastases.

Table 21. Applicant's Analysis of Deaths within 28 Days of Study Drug

	Palbociclib plus Fulvestrant (n= 345)	Placebo plus Fulvestrant (n=172)
Deaths within 28 Days	4 (1.2%)	3 (1.7%)
Progressive Disease	4	2
Study Drug Toxicity	0	0
Other	0	1[1]

[1]Intracerebral hemorrhage likely caused by AVM or single brain metastases not visible on baseline MRI
Source: 90-Day Safety Update, modified Table 14, page 50

The Applicant collected information concerning the cause of death in both a case report form (CRF) as well as detailed safety narrative summaries. Using the data from these sources provides very similar information to that above with the exception of the cause of death for subject 11661006, which is summarized below.

Subject 11661006 was a 69-year-old Caucasian woman who received palbociclib plus fulvestrant from Jul 8th, 2014 – (b) (6) Imaging on Aug 26th, 2014 revealed progressive disease and the investigator discontinued study treatment on Sept 2nd, 2014. The end of treatment visit was conducted on Sept 4th, 2014. CBC at that time was significant for ANC of 820/uL (down from 1400 on Aug 21st), platelets 90K /µL (down from 111) and hemoglobin of 8.8 g/dL (down from 9.3). The patient presented to the ED on (b) (6). She was febrile, hypotensive (BP 105/60), tachycardic (120 bpm), and blood culture was positive for E. coli. Labs were significant for neutropenia (350/µL), anemia (9.1g/dL) and thrombocytopenia (19,000/µL). Urine culture and chest x-ray were negative. The patient died on (b) (6). The investigator and sponsor considered the death unrelated to blinded therapy and secondary to "Deterioration of general condition due to disease progression."

Reviewer comments: *Subject 11661006 experienced a number of toxicities within 28 days of receiving palbociclib which were not reported in the AE dataset including febrile neutropenia*

and neutropenic sepsis. The only adverse event reported during this episode was Grade 5 "Deterioration of general condition" which does not capture the full extent of adverse events that occurred within 28 days of receiving study drug. An information request was sent to the Sponsor asking for further clarification, as it appeared from the clinical information the patient experienced neutropenic sepsis. The Sponsor responded with a detailed summary of the safety report, and reported that "After review of the patient file, the Investigator updated the cause of death to Neutropenic sepsis resulting in multi-organ failure which was reported as related to disease progression. The Investigator updated the original SAE report to reflect this change." Based on the information provided, it is possible that treatment with palbociclib contributed to this patient's death.

The additional patient deaths on study are summarized below.

Subject 10791002 was a 57-year-old Caucasian woman who received palbociclib plus fulvestrant from June 13, 2014 – July 25th, 2014. She was taken off study on July 25th secondary to progressive disease and received paclitaxel on [redacted] (b) (6) [redacted]. The following day she presented to the ED with coffee ground emesis and melenic stool. Laboratory workup revealed fulminant DIC with an INR of 12, presumably related to underlying malignancy vs. sepsis. On [redacted] (b) (6) her clinical status rapidly deteriorated with refractory shock despite pressors, worsening coagulopathy, and abdominal distention likely secondary to intraabdominal or retroperitoneal bleed. The patient died on [redacted] (b) (6) [redacted]. The Investigator and Sponsor considered the death to be unrelated to blinded therapy.

Reviewer comment: *Although we agree with the Investigator and Sponsor's Assessment of cause of death, there was no grade 5 AE in adverse event dataset in the initial application (only grade 4 DIC) even though the patient died within 28 days of receiving study drug. This error was corrected in the dataset submitted with the 90-Day Safety Update provided by the Sponsor.*

Subject 11371014 was a 36-year-old pre-menopausal Asian woman who received palbociclib plus fulvestrant from June 11th, 2014 to July 15th, 2014. CT scan on July 14th, 2014 revealed progressive disease. On [redacted] (b) (6) [redacted] she was admitted to the hospital with liver failure and the patient died on [redacted] (b) (6). The most likely cause of death was disease progression.

Subject 12891002 was a 72-year-old Caucasian woman with underlying arteriovenous malformation who received placebo from Aug 4th, 2014 to Sept 12th, 2014. On [redacted] (b) (6) [redacted] she presented to the hospital with headache and nausea/vomiting. Head CT showed a small acute hemorrhage and CT of chest/abdomen/pelvis revealed disease progression. Workup was negative. The patient was advised to discontinue aspirin and shortly prior to discharge, she experienced another intracranial hemorrhage. Head CT revealed further extension of the bleed with acute hydrocephalus. Her clinical condition deteriorated and she died on [redacted] (b) (6) [redacted]. ICH was reported as likely secondary to small underlying AVM or a hemorrhage secondary to a small metastatic deposit.

Subject 10011002 was a 38-year-old Caucasian woman who received palbociclib plus fulvestrant from Feb 3rd, 2014 to April 14th, 2014. Medical history was significant for bilateral malignant pleural effusions requiring pleurex catheter since May 2013. On April 15th, 2014 the patient was unable to ambulate secondary to dyspnea associated with progressive disease. She was transferred to inpatient hospice on [redacted] (b) (6) [redacted] and died on [redacted] (b) (6) [redacted]. The most likely cause of death was disease progression.

Subject 10511002 was a 61-year-old Caucasian woman who received placebo from June 17th, 2014 until her death [redacted] (b) (6). Her medical history was significant for refractory malignant pleural effusions. She died at home from respiratory distress. The most likely cause of death was disease progression.

There was one additional death reported with the 90 day Safety update (July 31st, 2015). The patient was randomized to placebo plus fulvestrant and died of disease progression.

The FDA analysis of Deaths within 28 days of study drug in Study 1023 as of July 31st, 2015 is shown below.

Table 22. FDA Analysis of Deaths within 28 Days of Study Drug

	Palbociclib plus Fulvestrant (n= 345)	**Placebo plus Fulvestrant (n=172)**
Deaths within 28 Days	4 (1.2%)	3 (1.7%)
DIC	1[1]	0
Disease progression	2	2
Intracerebral hemorrhage	0	1[2]
Neutropenic sepsis	1[3]	0

[1]DIC related to underlying malignancy or sepsis
[2]Intracerebral hemorrhage likely caused by AVM or single brain metastases not visible on baseline MRI
[3]Cause of death reported by Investigator was "Deterioration of general condition" due to underlying malignancy.
Source: 90-Day Safety Update

Reviewer comment: *The majority of deaths in Study 1023 were due to disease progression and no deaths were felt to be related to fulvestrant administration. None of the AEs leading to death were considered by the Investigator or the Sponsor to be related to palbociclib. However, one patient died of neutropenic sepsis within 28 days of receiving palbociclib. Based on the information provided, it is possible that treatment with palbociclib contributed to her death. A statement was added to Section 5.1 (Neutropenia under "Warnings and Precautions") of the palbociclib label indicating there was one death due to neutropenic sepsis in Study 1023.*

8.4.2. Serious Adverse Events

Information within the CSR, 90-Day Safety Update, Applicant's narrative summaries (CIOMS narratives), and the CRFs were used to analyze Serious Adverse Events in Study 1023. SAEs of any grade up to 28-days after the last dose of study therapy occurred in 53 (15.4%) patients receiving palbociclib plus fulvestrant and 31 (18%) of patients receiving placebo plus fulvestrant. No SAE occurred in >2% of patients and most SAEs reported were experienced by 1 patient each. The most frequently reported SAEs in the palbociclib plus fulvestrant arm were pyrexia (1.4%), neutropenia (1.2%), and pulmonary embolism (0.9%). The most frequently reported SAEs in the placebo plus fulvestrant arm were pleural effusion (1.7%), ascites (1.7%), pneumonia (1.2%), and pathological fracture (1.2%). Neutropenia and thromboembolic events will be discussed further below.

Table 23. Serious Adverse Events Occurring in >1 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant N=345	Placebo plus Fulvestrant N=172
Any	53 (15%)	31 (18%)
Pyrexia	5	1
Neutropenia	4	0
Pulmonary embolism	3	0
Deep vein thrombosis	2	0
Disease progression	2	0
Dyspnea	2	1
Febrile neutropenia	2	1
General physical health deterioration	2	0
Pharyngitis	2	0
Pleural effusion	2	3
Suicide attempt	2	0
Pneumonia	1	2
Ascites	0	3
Pathological Fracture	0	2

Includes data up to 28 days of last dose of study drug.
Source: 90-Day Safety Update, pages 53-54

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Patients were allowed to be withdrawn from the active treatment phase in the case of disease progression as per RECIST v 1.1, symptomatic deterioration, need for new or additional anti-cancer therapy not specified in the protocol, unacceptable toxicity, investigator's conclusion that discontinuing therapy is in the patient's best interest, lost to follow-up, patient choice to withdraw from treatment, withdrawal of patient consent, and death.

In patients receiving palbociclib plus fulvestrant, permanent discontinuation of protocol directed therapy associated with an adverse reaction occurred in 19 of 345 (5.5%) patients. A summary is provided in Table 30 below.

Table 24. Summary of TEAEs Associated with Permanent Discontinuation from Treatment in Patients Receiving Palbociclib plus Fulvestrant

	Palbociclib plus Fulvestrant N=345
Any	19 (5.5%)
Fatigue	2
Thrombocytopenia	2
Infections	2
Anemia	1
ALT increased	1
Bone pain	1
Breast mass	1
Disease progression	1
Drug-induced liver injury	1
Dyspnea	1
Endometrial cancer	1
Erysipelas	1
General physical health deterioration	1
Liver disorder	1
Nausea	1
Neutropenia	1
Pneumonia	1
Rectal cancer	1
Seizure	1
Suicide attempt	1
Vocal cord paralysis	1
White blood cell count decreased	1

Source: 90-day Safety Update, modified Table 17, page 57

In patients receiving placebo plus fulvestrant, permanent discontinuation of protocol directed therapy associated with an adverse reaction occurred in 6 of 172 (3.5%) patients. These TEAEs were gastric adenocarcinoma, anxiety, ascites, cerebral hemorrhage, pain, and sarcoidosis (1 patient (0.6%) each).

As of July 31st, 2015 a total of 128 patients (37%) in the palbociclib plus fulvestrant arm had their palbociclib dose reduced. One hundred eighteen patients (34%) had their dose reduced

from 125mg QD to 100mg QD, and 41 patients (12%) had their dose reduced from 125mg QD to 100mg QD and further to 75mg QD. In addition, 13 patients (3.8%) had their palbociclib dose regimen changed from schedule 3/1 to Schedule 2/2 (2 weeks on palbociclib treatment followed by 2 weeks off treatment). In the placebo plus fulvestrant arm, only three patients (1.7%) had their placebo dose reduced.

The most common AEs associated with dose reductions in the palbociclib plus fulvestrant arm were neutropenia (25%) followed by neutrophil count decreased (7%) and WBC count decreased (3%). The only Grade 4 events associated with palbociclib dose reduction were neutropenia and neutrophil count decreased, which occurred in 15 (4%) of patients. A summary of TEAEs associated with palbociclib/placebo dose reduction is shown in Table 31 below.

Dose reductions for fulvestrant were not allowed.

Table 25. Summary of TEAEs Associated with Dose Reduction of Palbociclib or Placebo Experienced by at Least 2 Patients in Either Treatment Arm, Sorted by Decreasing Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant N=345		**Placebo plus Fulvestrant N=172**	
	All Grades	Grade 3-4	All Grades	Grades 3-4
Any	124 (36%)	105 (30%)	3 (1.7%)	1 (0.6%)
Neutropenia	86	77	0	0
Neutrophil count decreased	24	23	0	0
WBC count decreased	9	5	1	0
Thrombocytopenia	4	1	0	0
Leukopenia	3	3	1	0
Stomatitis	2	1	0	0

Source: 90-Day Safety Update, modified Table 18, page 60.

The most common adverse events leading to a temporary discontinuation of treatment in the palbociclib plus fulvestrant arm were neutropenia (45.2%), neutrophil count decrease (14.5%), and WBC count decrease (8.1%). In the placebo plus fulvestrant arm, temporary discontinuations occurred most frequently due to pneumonia (2.3%) and influenza (1.2%). The incidence of dose delays is comparable to other studies of palbociclib.

8.4.4. Significant Adverse Events

The most common Grade 3/4 TEAEs observed following treatment with palbociclib plus fulvestrant were neutropenia and leukopenia. The rate of Grade 3/4 neutropenia was 66%

(56% Grade 3, 11% Grade 4) and the rate of Grade 3/4 leukopenia was 31% (30% Grade 3, 1% Grade 4) in the palbociclib plus fulvestrant arm. The rate of Grade 3/4 neutropenia and leukopenia was 1% each in the placebo plus fulvestrant arm. (Note: The cluster term Neutropenia used herein comprises MedDRA PTs Neutropenia and Neutrophil Count Decreased, and the cluster term Leukopenia used herein comprises MedDRA PTs Leukopenia and WBC Count Decreased).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 32 provides a summary of commonly reported treatment-related AEs regardless of severity grade experienced by at least 5% of patients in either treatment arm of Study 1023 as of July 31st, 2015 sorted by MedDRA System Organ Class then relative frequency. Overall, 94.2% of patients in the palbociclib plus fulvestrant arm and 67.4% of patients in the placebo plus fulvestrant arm experienced at least 1 TEAE.

Table 26. Summary of Treatment Emergent AEs in Study 1023

System Organ Class Preferred Term	**Palbociclib plus Fulvestrant (N=345)**			**Placebo plus Fulvestrant (N=172)**		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and Infestations						
Infections[1]	47.0	2.6	0.6	30.8	2.9	0
Blood and Lymphatic System Disorders						
Febrile neutropenia	0.9	0.9	0	0.6	0	0.6
Neutropenia[2]	83.2	55.9	10.7	4.1	0.6	0
Leukopenia[3]	53.0	29.9	0.6	5.2	0.6	0.6
Anemia[4]	29.3	3.2	0	12.2	1.2	0
Thrombocytopenia[5]	22.6	1.7	0.6	0	0	0
Eye disorders						
Lacrimation increased	6.4	0	0	1.2	0	0
Vision blurred	5.8	0	0	1.2	0	0
Dry eye	3.8	0	0	1.7	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	15.7	0.9	0	8.1	0.6	0
Nervous System disorders						
Headache	26.1	0.6	0	20.9	0	0

Dysgeusia	6.7	0	0	2.9	0	0
Gastrointestinal disorders						
Nausea	33.9	0	0	27.9	1	0
Stomatitis[6]	28.4	0.6	0	13.4	0	0
Diarrhea	23.5	0	0	19.2	1.2	0
Constipation	20.0	0	0	15.7	0	0
Vomiting	18.8	0.6	0	15.1	0.6	0
Dry mouth	5.8	0	0	5.8	0	0
Skin and subcutaneous disorders						
Alopecia	18.0[7]	NA	NA	6.4[8]	NA	NA
Rash [9]	16.8	0.6	0	6.4	0	0
Dry Skin	6.1	0	0	1.2	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	6.7	0	0	1.7	0	0
General Disorders and administrative site conditions						
Fatigue	41.2	2.3	0	29.1	1.2	0
Pyrexia	12.8	0.3	0	5.2	0	0
Arthralgia	15.9	0.6	0	18.0	0	0
Back pain	15.9	1.1	0	17.4	1.7	0
Asthenia	7.5	0	0	5.2	0.6	0
Injection site pain	6.7	0.3	0	10.5	0	0
Myalgia	4.9	0	0	5.2	0	0
Vascular disorders						
Hot flush	15.7	0	0	16.9	0.6	0

[1] Infection includes all PTs that are part of the System Organ Class Infections and infestations.
[2] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.
[3] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.
[4] Anemia includes the following PTs: Anemia, hemoglobin decreased, hematocrit decreased.
[5] Thrombocytopenia includes the following PTs: Thrombocytopenia, platelet count decreased.
[6] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
[7] Grade 1 events – 17%; Grade 2 events – 1%.
[8] Grade 1 events – 6%
[9] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.
Source: AE dataset submitted with original application and 90-Day Safety Update (ADVERS.xpt)

The most frequently reported TEAEs (i.e. ≥ 20% of patients) in the palbociclib plus fulvestrant arm were neutropenia (83%), leukopenia (53%), infections (47%), fatigue (41%), nausea (34%),

anemia (29%), stomatitis (28%), headache (28%), diarrhea (24%), thrombocytopenia (23%), and constipation (20%). The most frequently reported TEAEs (i.e. ≥ 20% of patients) in the placebo plus fulvestrant arm were infections (31%), fatigue (29%), and nausea (28%). The following common TEAEs were reported substantially more frequently (i.e. ≥ 10% difference in frequency) for the palbociclib plus fulvestrant arm than for the placebo plus fulvestrant arm: neutropenia, leukopenia, anemia, thrombocytopenia, infections, fatigue, stomatitis, alopecia, and rash.

Reviewer's Comment:
In early February the Sponsor submitted results of their quality control audit of the 90-Day Safety Update. Based on this audit, the final fulvestrant label contains numbers slightly different from those reported in Table 32 *above. These minor changes are summarized below:*

- *Incidence of Grade 3 Neutropenia in the palbociclib arm was 55% (down from 56%).*
- *Incidence of Anemia (all grades) was 13% in the placebo arm (up from 12%).*
- *Incidence of Grade 3 Anemia in the placebo arm was 2% (up from 1%).*
- *Incidence of Vision blurred (all grades) in the placebo arm was 2% (up from 1%).*

There are minor differences in the adverse drug reaction tables included in the palbociclib label and fulvestrant label due to the inclusion of adverse drug reactions in the fulvestrant label that have previously been reported with fulvestrant and occurred more frequently in the fulvestrant plus placebo arm compared to the fulvestrant plus palbociclib arm. The following adverse drug reactions were added to the fulvestrant label: arthralgia, back pain, injection site pain, and hot flush. Given that the palbociclib label listed only adverse drug reactions (as opposed to TEAEs), there was no frequency cut-off employed for Table 6 in the palbociclib label. Rather, a TEAE was included as an adverse drug reaction if after careful examination by the Sponsor and the Agency, it was determined to be reasonably associated with palbociclib.

8.4.6. Laboratory Findings

Overall, hematologic laboratory abnormalities were more commonly observed for patients in the palbociclib plus fulvestrant arm, compared with those in the placebo plus fulvestrant arm. Almost all patients in the palbociclib plus fulvestrant arm with hematologic laboratory tests available for evaluation had abnormal absolute neutrophil counts (96.2%) and white blood cell counts (98.5%). With the exception of abnormal absolute neutrophil count and white blood cells, most abnormal hematologic findings were Grade 1/2 severity. ANC counts of Grade 3 severity were observed for more than half of the patients (56%) in that treatment arm; in addition, Grade 4 neutrophil counts were observed for 11% of the patients receiving palbociclib plus fulvestrant.

Table 27. Summary of Abnormal Clinical Hematology Laboratory Findings by Maximum Severity Grade in Study 1023

	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant

	(N=345)		(N=172)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
WBC decreased	99	46	26	1
Neutrophils decreased	96	67	14	1
Anemia	78	3	40	2
Platelets decreased	62	3	10	0

Source: 90-Day Safety Update, modified Table 36, page 94

Hematologic laboratory data were also reviewed in terms of shifts from Grade ≤2 at baseline to Grade ≥3 post-baseline. Overall, more shifts in clinical hematology test results were observed in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm, with the majority of results in the palbociclib plus fulvestrant arm shifting from Grade ≤2 at baseline to Grade 3 post-baseline. Most shifts from Grade ≤2 at baseline to Grade 4 post-baseline were observed in that treatment arm for absolute neutrophil counts (10.6%). A few shifts in neutrophil counts from Grade ≤2 at baseline to Grade 4 post-baseline were also observed for patients in the placebo plus fulvestrant arm (1.2%).

Reviewer comments: *Overall, the abnormal clinical hematology laboratory findings are generally consistent with the corresponding abnormal clinical findings reported as TEAEs.*

Abnormal clinical chemistry findings observed in this study as of July 31st, 2015 are summarized by maximum severity grade in Table 34.

Table 28. Summary of Abnormal Clinical Chemistry Laboratory Findings by Maximum Severity Grade in Study 1023

	Palbociclib plus Fulvestrant (N=345)		Placebo plus Fulvestrant (N=172)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
ALT	36	2	34	0
Alkaline phosphatase	33	1	40	1
AST	43	4	48	4
Bilirubin	9	1	7	2
Creatinine	94	1	83	0
Hypercalcemia	14	<1	12	0
Hyperkalemia	12	1	9	1
Hypermagnesemia	11	1	11	1
Hypernatremia	13	0	12	0
Hypoalbuminemia	21	0	21	1
Hypocalcemia	26	0	15	1

Hypokalemia	16	0	15	0
Hypomagnesemia	21	0	16	0
Hyponatremia	21	3	18	2

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.
Source: 90-Day Safety Update

Abnormal clinical chemistry laboratory findings were also reviewed in terms of shifts from Grade ≤2 at baseline to Grade ≥3 post-baseline. Such shifts were infrequent in either treatment arm. A shift from Grade ≤2 at baseline to Grade 4 post-baseline was observed for one patient in the palbociclib plus fulvestrant arm; this patient had a shift in total bilirubin from outside of the Grading range at baseline to Grade 4 post-baseline.

Preclinical evidence suggested that ocular toxicities in patients receiving palbociclib may be due to altered glucose metabolism. In order to further explore this association, glycosylated hemoglobin levels were measured and reported after the 2nd amendment. As of July 31st, 2015 there was only one case of elevated HgbA1c, and this patient received placebo plus fulvestrant arm.

Reviewer comments:
Overall, there were comparable proportions of patients between the treatment arms with abnormal clinical chemistry laboratory values based on the data reported. Our review of the effect of palbociclib on glucose metabolism is limited due to lack of information provided by the Sponsor. Despite the preclinical evidence suggesting that ocular toxicities in patients receiving palbociclib may be due to altered glucose metabolism, serum glucose measurements were not recorded in this study. However, it is reassuring that there were no cases of elevated HgbA1c reported in the palbociclib arm as of July 31st, 2015.

8.4.7. Vital Signs

Overall, the mean and median blood pressure, pulse rate, and weight were well balanced between the two treatment arms at baseline. The median values for each vital sign measurement in each treatment cycle were generally comparable between the treatment arms. No clinically relevant changes from baseline in any of the vital sign measurements were observed in either treatment arm as of July 31st, 2015.

8.4.8. Electrocardiograms (ECGs)

Twelve-lead triplicate ECG recordings were performed in patients in Study 1023 at screening and at the end of treatment. Clinically relevant ECG findings observed in Study 1023 were reported as TEAEs and discussed in Sections 8.4.1 and 8.4.2.

8.4.9. QT

A QTc analysis was performed on the CTc Analysis Set as part of the original palbociclib

submission. Palbociclib at 125mg QD did not substantially affect the QTc interval.

In Study 1023 one patient in the palbociclib plus fulvestrant arm experienced an SAE of Grade 3 Electrocardiogram QT prolonged that coincided with a Grade 2 SAE of pericarditis and resolved to Grade 1 within 2 days. Palbociclib therapy was temporarily discontinued in response to these events and was subsequently restarted, although at a reduced dose of 100mg QD. No additional cases of Electrocardiogram QT prolonged were reported in Study 1023 as of July 31st, 2015.

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Neutropenia

Consistent with the pharmacologic activity of palbociclib (i.e. cell cycle inhibition), myelosuppression is observed in clinical studies of palbociclib. Neutropenia reported in Study 1023 comprises the MedDRA PTs of Neutropenia and Neutrophil count decreased. The data based on clinical laboratory tests of absolute neutrophil counts will also be reported here.

The frequency of neutropenia in Study 1023 was substantially higher in the palbociclib plus fulvestrant arm (83%) compared to the placebo plus fulvestrant arm (4%). The majority of neutropenia events in the palbociclib arm were Grade 3 (56%) or Grade 4 (11%) and most were considered treatment related. In the palbociclib plus fulvestrant arm, three (0.9%) patients experienced febrile neutropenia and one (0.3%) patient experienced Grade 4 neutropenia associated with permanent discontinuation from treatment. Most cases of Grade 3/4 neutropenia were managed by dose reduction, dosing interruption, and/or treatment cycle delay. Only one case of neutropenia led to treatment discontinuation.

Based on clinical laboratory findings in Study 1023, 326/339 patients (96%) in the palbociclib plus fulvestrant had abnormal absolute neutrophil counts (ANC), including 189 (56%) with Grade 3 decreases and 36 (11%) with Grade 4 decreases. In comparison, 23/167 (14%) patients in the placebo plus fulvestrant arm had abnormal ANC of whom none had Grade 3 decreases and two (1.2%) had Grade 4 decreases.

Baseline characteristics among patients in the palbociclib plus fulvestrant arm who had or did not have abnormal absolute neutrophil counts of Grade 3/4 maximum severity were comparable as demonstrated in Table 21 below.

Table 29. Baseline Characteristics for Subjects with and without Grade 3/4 Neutropenia

	Palbociclib plus Fulvestrant (N=345)		Placebo plus Fulvestrant (N=172)	
	With Grade 3/4 Neutropenia (n=225)	Without Grade 3/4 Neutropenia (n=120)	With Grade 3/4 Neutropenia (n=2)	Without Grade 3/4 Neutropenia (N=170)
Subjects with prior chemo, %				
Yes	72	72	100	78
No	27	28	0	22
Age, %				
≤ 65	80	74	100	77
>65	20	26	0	24
ECOG PS, %				
0	59	60	50	67
1	41	40	50	33

Source: 90-Day Safety Update, modified Table 14.3.2.1.4.2.

The shortest time from first dose of palbociclib/placebo to onset for neutropenia of any severity grade was similar between the palbociclib plus fulvestrant arm (13 days) and the placebo plus fulvestrant arm (15 days). In the palbociclib plus fulvestrant arm, the median time from first dose of palbociclib to onset of first neutropenia episode of any severity grade was shorter than one treatment cycle (Any grade - 15 days; Grade ≥ 2 - 15 days; Grade ≥ 3 - 16 days; Grade 4 - 19 days). In the placebo plus fulvestrant arm, the median times from first dose to onset of first neutropenia episode of any grade severity was 211 days.

The median duration of any grade neutropenia by patient (i.e. duration of all episodes combined) reported in the palbociclib plus fulvestrant arm was 179 (3-573) days across all cycles, while the median duration of Grade ≥ 3 neutropenia and Grade 4 neutropenia across all cycles was 21 (1-167) days and 10.5 (2-28) days, respectively. The duration of neutropenia by patient regardless of severity grade was longer than 1 treatment cycle in most patients (94%) who had neutropenia in the palbociclib plus fulvestrant arm. The median duration of any grade neutropenia by episode reported in the palbociclib plus fulvestrant arm was 15 (1-287) days. Overall, neutropenia persisted for longer than half of total treatment duration, as the median ratio of duration of any grade neutropenia to duration of treatment was 69.5% (2.8%-160%) for patients in the palbociclib plus fulvestrant arm. The median time to recovery (i.e. >1500 ANC) from lowest neutrophil count among patients with Grade ≥ 3 neutropenia in the palbociclib arm was 36 (3-449) days. Forty-two (12.2%) patients were treated with a colony stimulating factor (e.g. filgrastim, pegfilgrastim) for neutropenia.

Febrile neutropenia was experienced by three patients in the palbociclib plus fulvestrant arm of

Study 1023 (Cycle 1 Week 3, Cycle 5 Week 4, and Cycle 5 Week 5). All three cases of febrile neutropenia were Grade 3 and considered to be related to treatment with palbociclib. One patient in the placebo plus fulvestrant arm of this study experienced febrile neutropenia of Grade 4 severity, and this event was not considered to be related to treatment.

No TEAEs of neutropenic sepsis were reported in either treatment arm of Study 1023. However, as discussed previously there was one case of treatment emergent fatal neutropenic sepsis and multi-organ failure in a patient receiving palbociclib plus fulvestrant (Subject No. 11661006). Neither the Investigator nor the Sponsor considered these events to be related to treatment.

Reviewer comment: *Although neutropenia is very common on the palbociclib arm, it is reassuring that most cases resolved within 2-3 weeks without significant complications. There was no significant association between fulvestrant exposure and neutropenia.*

8.5.2. Infections

Overall, more patients in the palbociclib plus fulvestrant arm experienced TEAEs within the MedDRA SOC Infections and Infestations as of the July 31st, 2015 cut-off (47% vs. 34%, respectively). The TEAEs coding to PTs within the SOC Infections and Infestations experienced by at least two patients in either treatment arm of Study 1023 are summarized in Table 22 below.

Table 30. Infections Experienced by ≥ 2 Patients in Study 1023

	Palbociclib plus Fulvestrant (N=345)		**Placebo plus Fulvestrant (N=172)**	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any	162 (47%)	11 (3%)	53 (31%)	5 (3%)
Nasopharyngitis	45	0	14	0
URI	32	2	12	0
UTI	26	0	11	1
Bronchitis	11	0	3	0
Rhinitis	10	0	2	0
Influenza	9	0	8	0
Conjunctivitis	8	1	3	0
Sinusitis	8	0	2	0
Cystitis	6	0	2	0
Oral Herpes	6	0	1	0
Pneumonia	6	1	4	1
Respiratory Tract Infection	5	0	1	0

Gastroenteritis	5	0	0	0
Pharyngitis	5	1	0	0
Tooth infection	5	0	0	0
Eye infection	4	0	0	0
Herpes Simplex	4	0	0	0
Paronychia	4	0	0	0
Candida infection	3	0	0	0
Cellulitis	3	1	0	0
Gingivitis	3	0	0	0
Gastrointestinal infection	2	0	1	1
Erysipelas	2	1	0	0
Furuncle	2	0	0	0
Herpes Zoster	2	0	1	0
Lymphangitis	2	0	0	0
Oral Candidiasis	2	0	0	0
Tooth abscess	2	0	0	0
Viral infection	2	1	1	0
Gastroenteritis viral	1	0	2	0

URI: upper respiratory tract infection; UTI: urinary tract infection
Source: AE dataset submitted with 90-Day Safety Update (ADVERS.xpt)

No TEAEs of neutropenic infection were reported by the Sponsor in either treatment arm of Study 1023. However, 50 (14%) patients in the palbociclib plus fulvestrant arm were reported to have Grade 3/4 neutropenia overlapping with any grade TEAEs within SOC Infections and Infestations. No patients in the placebo plus fulvestrant arm were reported to have Grade 3/4 neutropenia overlapping with any grade TEAEs within SOC Infections and Infestations. Two patients in the palbociclib arm experienced a Grade 3 or 4 infection in the setting of Grade 3 neutropenia and their narratives are summarized below. There were no cases of Grade 3 or 4 infection in the setting of Grade 4 neutropenia.

Grade 4 Cellulitis in the Setting of Grade 3 Neutropenia
Subject 10071003 was a 44-year-old Caucasian woman who received palbociclib from Nov 21st, 2013 – Dec 20th, 2013. She had no significant past medical history other than breast cancer. On [redacted] she was hospitalized for cellulitis of the left arm in the setting of Grade 3 Neutropenia. Palbociclib was withdrawn temporarily and she was treated with Keflex 500mg bid. She was discharged on [redacted] and she recovered on Jan 15th, 2014. The Investigator and Sponsor agreed there was not a reasonable possibility that the event was related to palbociclib. The patient was withdrawn from study on Jan 15th, 2014 due to progressive disease.

Grade 3 Erysipelas in the Setting of Grade 3 Neutropenia Leading to Permanent

Discontinuation Subject 11581002 was a 70-year-old woman of unspecified ethnicity who received palbociclib from Mar 13th, 2014 – July 15th, 2014. On July 15th, 2014 patient experienced swelling, pain, and erythema of right lower extremity in the setting of Grade 3 Neutropenia. She was diagnosed with erysipelas and hospitalized on [redacted] (b) (6) [redacted]. She was treated with IV benzylpenicillin and discharged on [redacted] (b) (6) [redacted] on an oral antibiotic regimen consisting of augmentin, phenethicillin, and rifampin. On July 29th, 2014 the erysipelas showed no improvement and antibiotic regimen was switched to ciprofloxacin. On Aug 5th, 2014, patient began to show improvement in erysipelas. The patient was subsequently withdrawn from study due to a greater than three week treatment delay. The Investigator and Sponsor agree that there was a reasonable possibility that the event was related to palbociclib.

An evaluation of neutropenia based on clinical laboratory findings overlapping with TEAEs coding to PTs within the SOC Infections and Infestations is shown in Table 23 below.

Table 31. Summary of Neutropenia (Based on Clinical Laboratory Findings) Overlapping with TEAEs within the MedDRA SOC Infections and Infestations

	Palbociclib plus Fulvestrant (N=345)	**Placebo plus Fulvestrant (N=172)**
Any grade neutropenia	326	18
Overlapping with any Grade TEAEs within the SOC Infections and Infestations		
Yes	132 (41%)	2 (11%)
No	194 (59%)	16 (89%)
Overlapping with Grade 3/4 TEAEs within the SOC Infections and Infestations		
Yes	8 (2.5%)	0
No	318 (97.5%)	18 (100%)
Grade 3/4 Neutropenia	225	2
Overlapping with any Grade TEAEs within the SOC Infections and Infestations		
Yes	50 (22%)	0
No	127 (78%)	2 (100%)
Overlapping with Grade 3/4 TEAEs within the SOC Infections and Infestations		
Yes	3 (1%)	0
No	222 (99%)	2 (100%)

Source: 90-Day Safety Update, modified Table 29, page 79

As shown in Table 23 above, nearly half of patients (41%) who had a laboratory finding of neutropenia in the palbociclib plus fulvestrant arm experienced a concomitant TEAE within the MedDRA SOC Infections and Infestations. A total of 8 patients (2.5%) with any severity grade neutropenia experienced a concomitant Grade 3/4 TEAE within this SOC. The majority of patients with Grade 3/4 Neutropenia (78%) in the palbociclib plus fulvestrant arm did not experience concomitant TEAEs within the SOC Infections and Infestations, with only three patients (1.3%) experiencing a concomitant Grade 3/4 TEAE with this SOC (Grade 3 Erysipelas and Grade 4 Cellulitis both described above, as well as a Grade 3 Upper respiratory tract infection).

Reviewer comment: *It is reassuring that the overall rates of Grade 3/4 infections are low and only 3 patients (<1%) experienced a Grade 3 or 4 infection in the setting of concomitant Grade 3 or 4 neutropenia.*

8.5.3. Thrombocytopenia

Thrombocytopenia was reported in 86 (25%) patients receiving palbociclib plus fulvestrant in Study 1023, while no cases of thrombocytopenia were reported in the placebo plus fulvestrant arm. As shown in Table 32, most cases were of Grade 1/2 severity. Neither Grade 3 nor Grade 4 thrombocytopenia events were associated with bleeding episodes (based on hemorrhagic terms). One patient experiencing Grade 3 thrombocytopenia was permanently discontinued from treatment, while three patients with Grade 3 thrombocytopenia and one patient with Grade 4 thrombocytopenia had their dose reduced/interrupted or had their treatment cycle delayed.

Reviewer comment: *Given that the presence of thrombocytopenia may preclude the administration of fulvestrant, it is reassuring that there were very few cases of Grade 3 thrombocytopenia and no cases of grade 4 thrombocytopenia in the palbociclib plus fulvestrant arm.*

8.5.4. Eye Disorders

Eye disorders were more frequently reported in patients in the palbociclib plus fulvestrant arm (22%) than in the placebo plus fulvestrant arm (11%). As shown in Table 24 below, the most frequently reported TEAEs within the SOC Eye Disorders for the palbociclib plus placebo arm were Lacrimation increased (6.4%), Vision blurred (5.8%), Dry eye (3.8%), and Eye irritation (2.0%). The most frequently reported TEAEs within this SOC in the placebo plus fulvestrant arm were Dry eye (1.7%), Lacrimation increased (1.2%) and Vision blurred (1.2%). No grade 3/4 Eye disorders were reported for either treatment arm.

Table 32. Summary of TEAEs within the MedDRA SOC Eye Disorders Experienced by ≥ 2 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant Arm

	Palbociclib plus Fulvestrant (N=345)	Placebo plus Fulvestrant (N=172)
Any	77 (22%)	18 (11%)
Lacrimation increased	22	2
Vision blurred	20	2
Dry eye	13	3
Eye Irritation	7	0
Visual impairment	6	1
Diplopia	5	0
Eye Pain	3	2
Vitreous floaters	3	2
Cataract	2	0
Eye pruritus	2	0
Retinal degeneration	2	0
Visual acuity reduced	2	0

Source: AE dataset with 90-Day Safety Update (ADVERS.xpt)

Hyperglycemia

Nonclinical findings in rats support the notion that cataracts/lens degeneration was associated with altered glucose metabolism (glycosuria and/or hyperglycemia) in the setting of palbociclib exposure. A further association was found between glucose metabolism and pancreatic islet vacuolation leading to beta cell depletion and decreases in serum insulin and C-peptide. Reversibility was not established for the changes in glucose homeostasis or the effects on the pancreas and eye following a 3-month recovery period.

As of July 31st, 2015 a total of five patients (1.4%) in the palbociclib plus fulvestrant arm and four patients (2.3%) in the placebo plus fulvestrant arm were reported to experience hyperglycemia. In each treatment arm, all but one TEAE of hyperglycemia were of Grade 1 severity. The remaining patients (one in each treatment arm) experienced Grade 3 hyperglycemia. Diabetes mellitus (grade 1) was experienced by one patient (0.3%) in the palbociclib plus fulvestrant arm and an increase in HgbA1c was experienced by 1 patient (0.6%) in the placebo plus fulvestrant arm. None of the patients who experienced cataracts in the palbociclib plus fulvestrant arm experienced any hyperglycemia-related events.

8.5.5. Venous Thromboembolic Events

As of July 31st, 2015, there were a total of 3 pulmonary embolisms reported in Study 1023, all 3 of which were in the palbociclib plus fulvestrant arm and all three were categorized as SAEs. Two of three were asymptomatic and discovered incidentally. Each event is summarized below.

Subject 11661005 is a 50-year-old Caucasian woman who began therapy with palbcociclib plus fulvestrant on June 21st, 2014. On Sept 18th, 2014 a Chest CT was performed due to persistant complaints of dyspnea. CT revealed moderate segmental and subsegmental PE with right lower lobe predominance. The patient was treated with anticoagulation and no action was taken with blinded therapy and fulvestrant in response to the event. The patient recovered from the event on Jan 27th, 2015.

Subject 10101005 is a 65-year-old Caucasian woman who began therapy with palbociclib plus fulvestrant on Apr 17th, 2014. On Aug 3rd a schedule (16-week) CT of chest/abdomen/pelvis) revealed a small pulmonary embolus. The PE was an incidental finding and the patient was asymptomatic. The patient was treated with anticoagulation and no action was taken with blinded therapy and fulvestrant in response to the event. The patient recovered from the event on Aug 5th, 2014.

Subject 12611004 is a 58-year-old woman of unspecified ethnicity who began therapy with palbociclib plus fulvestrant on Jun 4th, 2014. On July 22nd, the patient went off treatment due to symptomatic disease progression. On [redacted] (b) (6) a CT of chest/abdomen/pelvis (as part of end-of-treatment evaluation) revealed a filling defect within the right main pulmonary artery, extending to the segmental branches of the right limb. The patient was asymptomatic. She was admitted for further management and treated with anticoagulation. The patient recovered from the event on May 18, 2015.

Reviewer comment: *A similar numerical increase in rate of PE with palbociclib was also observed in Study 1003 (4.8% in palbociclib plus letrozole arm vs. 0% in letrozole alone arm) and ongoing Study 1008, including 2 deaths due to blinded treatment in the latter. Taken together, these results suggest that palbociclib may increase the risk of pulmonary embolism. The palbociclib label includes pulmonary embolism under "Warnings and Precautions."*

Deep venous thrombosis was experienced by two patients in the palbociclib plus fulvestrant arm. In addition, Embolism, Subclavian vein thrombosis, and Vena cava thrombosis were experienced by 1 patient each in the palbociclib arm. In the placebo plus fulvestrant arm, Pelvic venous thrombosis was experienced by 1 patient. No other venous thromboembolic events were experienced by patients receiving placebo in Study 1023 as of the July 31st, 2015 cut-off.

8.5.6. Skin and Subcutaneous Tissue Disorders

Skin and subcutaneous tissue disorders were more frequently reported in patients in the palbociclib plus fulvestrant arm (46%) than in the placebo plus fulvestrant arm (21%). As shown in Table 25 below, the most frequently reported TEAEs within the SOC Skin and Subcutaneous Tissue Disorders for both arms were Alopecia, Rash, Pruritus, and Dry skin. Only two events in the palbociclib plus fulvestrant arm were considered Grade 3; the remaining TEAEs were Grade 1 or 2. Subject 11821001 experienced a Grade 3 rash that lasted 12 days and required a

treatment interruption, and Subject 12141003 experienced Grade 3 rash maculo-papular that lasted 8 days and required a dose reduction. No Grade 3/4 Skin and subcutaneous tissue disorders were reported in the placebo plus fulvestrant arm.

Table 33. Summary of TEAEs within the MedDRA SOC Skin and Subcutaneous Tissue Disorders Experienced by ≥ 2 Patients Sorted by Descending Frequency in the Palbociclib plus Fulvestrant arm

	Palbociclib plus Fulvestrant (N=345)	Placebo plus Fulvestrant (N=172)
Any	159 (46%)	36 (21%)
Alopecia	62	11
Rash[1]	59	11
Pruritus	26	11
Dry Skin	21	2
Erythema	9	2
Night sweats	9	1
Skin lesion	6	1
Hyperhidrosis	5	2
Pain of skin	5	0
Palmar-plantar erythrodysaesthesia syndrome	5	1
Skin ulcer	4	0
Ingrowing nail	3	0
Onychoclasis	3	0

[1] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.
Source: AE dataset with 90-Day Safety Update

8.6. Safety Analyses by Demographic Subgroups

Age
Safety data reported in Study 1023 were analyzed by age (<65 and ≥65 years old). The overall frequencies of TEAEs, SAEs, and AEs associated with permanent discontinuation were generally comparable between the two age groups within the palbociclib plus fulvestrant arm. In addition, the overall rates of dose reduction/modification and temporary discontinuation from treatment associated with TEAEs were also generally comparable between the two age groups in that treatment arm.

In the palbociclib plus fulvestrant arm of Study 1023, nausea was the only TEAE experienced substantially more frequently (i.e. >10% difference in TEAE frequency) by patients younger than 65 years of age (37.1%) than by those 65 years of age or older (24.4%). Alopecia and Dyspnea were the TEAEs experienced substantially more frequently by patients 65 years of age or older

(25.6% and 23.3%, respectively) than by those younger than 65 years of age (15.4% and 10.0%, respectively). Most hematologic TEAEs were reported substantially more frequently in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm regardless of age group.

Sex

No analysis of palbociclib plus fulvestrant safety data with regard to patients' were performed on the data from Study 1023 since all patients in this study were women. However, palbociclib has been studied in 85 males as part of Studies 1001 (n=36; advanced solid tumor malignancy), 1002 (n=14; mantle cell lymphoma), 1004 (n=30; multiple myeloma), 1010 (Phase1, Part1 n=5; advanced solid tumor malignancy) as well as in several Investigator-Initiated Research (IIR) studies. Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients) from Studies 1001, 1002, and 1003, gender had no effect on the exposure of palbociclib. In addition, the safety profile in male patients has been consistent with the safety profile seen in palbociclib across the development program.

Race

Safety data from Study 1023 were also analyzed by Race (White, Black, Asian, and Other). Most patients participating in either treatment arm of this study were White (72.6% in the palbociclib plus fulvestrant arm and 76.4% in the placebo plus fulvestrant arm). The second largest race group in this study was Asian (21.3% in the palbociclib plus fulvestrant arm and 17.8% in the placebo plus fulvestrant arm). Because of the small number of patients whose race was Black (N = 12 in the palbociclib plus fulvestrant arm and N = 8 in the placebo plus fulvestrant arm), no reliable observations or comparisons could be made regarding the safety profile of palbociclib plus fulvestrant in patients of that race.

A comparison of data between White and Asian patients within the palbociclib plus fulvestrant arm is summarized in Table 26. There was a higher overall Grade 3/4 TEAE frequency in Asian patients (94.5%) than in White patients (71.3%), although the overall TEAE frequency was similar between the 2 race groups (98.4% for White patients and 100% for Asian patients). These differences were not appreciated in the placebo plus fulvestrant arm.

Table 34. Summary of TEAE by Race Group Reported in the Palbociclib plus Fulvestrant Arm in Study 1023

	Palbociclib plus Fulvestrant (N=345) Number (%) of Patients	
Patient category	White (N=251)	Asian (N=73)
Any TEAE	247 (98.4)	73 (100)
Grade 3/4 TEAE	179 (71.3)	69 (94.5)
Grade 5 TEAE	2 (0.8)	1 (1.4)
Any SAE	36 (14.3)	13 (17.8)
Discontinued palbociclib due to TEAEs	12 (4.8)	3 (4.1)

Discontinued fulvestrant due to TEAEs	10 (4.0)	3 (4.1)

Source: 90-Day Safety Update, modified Table 47, page 111

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review.

8.8.2. Human Reproduction and Pregnancy

See Pharmacology/Toxicology Review.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
No accidental overdoses were reported in Study 1023.

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

Withdrawal and Rebound
A formal study has not been conducted by the applicant to investigate withdrawal and/or rebound.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Fulvestrant has been approved as monotherapy in the US since 2002 for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer who disease has progressed following antiestrogen therapy. Palbociclib received accelerated approval in February 2015 in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative, advanced breast cancer as initial endocrine-based therapy for their

metastatic disease. Overall, approximately 10,000 patients received palbociclib in the US post-marketing setting from February 2015 – July 2015 (excluding patients in clinical trials receiving drug outside of commercial channels and patients receiving drug through compassionate use mechanism). The most recent quarterly NDA paper was submitted in December 2015 and covered the period from Aug 3rd, 2015 through Nov 2nd, 2015. During that period 248 safety reports were submitted. In addition, 146 initial and 102 follow up 15 Day Alerts were submitted during this period.

Reviewer comment: *The cumulative postmarket safety data of palbociclib and fulvestrant reviewed did not raise any new safety concerns.*

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable

8.10. Additional Safety Issues From Other Disciplines

Not applicable

8.11. Integrated Assessment of Safety

The safety profile of fulvestrant plus palbociclib for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer is generally tolerable, with adverse reactions manageable through the use of palbociclib dose reduction, temporary treatment discontinuation, and/or standard medical care. No new safety concerns for either drug have been identified based on the cumulative safety data submitted in this sNDA.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this sNDA.

10 Labeling Recommendations

10.1. Prescribing Information

Please see final Faslodex PI.

Patient Labeling

Please see final patient labeling.

10.3. Nonprescription Labeling

This is not applicable for this sNDA.

11 Risk Evaluation and Mitigation Strategies (REMS)

None

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

None

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

None

11.3. Recommendations on REMS

None

12 Postmarketing Requirements and Commitments

None.

13 Appendices

13.1. References

1. Faslodex drug label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021344s019s020lbl.pdf
2. Flaherty KT, LoRusso PM, DeMichele A, et al. Phase I, Dose-Escalation Trial of the Oral Cyclin-Dependent Kinase 4/6 Inhibitor PD 0332991, Administered Using a 21-Day Schedule in Patients with Advanced Cancer. Clin Cancer Res; 18(2):568-576. (2012)
3. Schwartz GK1, LoRusso PM, Dickson MA, et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). Br J Cancer. 2011 Jun 7;104(12):1862-8.
4. DeMichele A, Clark AS, Tan KS, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin Cancer Res; 21(5):995-1001. (2015)
5. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35. doi: 10.1016/S1470-2045(14)71159-3. Epub 2014 Dec 16.
6. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015 Jul 16;373(3):209-19. doi: 10.1056/NEJMoa1505270. Epub 2015 Jun 1.
7. Siegel R., Miller K., Jemal A. Cancer Statistics, 2016. Cancer J Clin ; 66 7-30. (2016)
8. SEER Cancer Statistics Database: Breast Cancer http://seer.cancer.gov/statfacts/html/breast.html (2016)
9. Lim E, Metzger-Filho O, Winer EP. The natural history of hormone receptor-positive breast cancer. Oncology; 26(8), 688-94. (2012)
10. Singh JC, Jhaveri K, Esteva FJ. HER2-positive advanced breast cancer: optimizing patient outcomes and opportunities for drug development. British J of Cancer; 111, 1888-1898. (2014)
11. Burstein HJ. The distinctive nature of HER2-positive breast cancer. N Engl J Med; (353), 1652-54. (2005)
12. Beaver J., Amiri-Kordestani L., Chen R., et al. FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer. Clin Cancer Res; 21, 4760-6. (2015)

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study A5481023 (PALOMA-3)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 1232		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUPARNA B WEDAM
02/19/2016

AMANDA J WALKER
02/19/2016

ERIK W BLOOMQUIST
02/19/2016

SHENGHUI TANG
02/19/2016

LALEH AMIRI KORDESTANI
02/19/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

CHEMISTRY REVIEW(S)

OFFICE OF LIFE CYCLE PRODUCTS
DPMA I, BRANCH I

Review of Chemistry, Manufacturing, and Controls

Clinical Review Division: Oncology Drug Products (HFD-150)

NDA#: 21-344	**REVIEW#.** 1	**REVIEW DATE:**	02/02/2016
SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED**
S-026 (SE)	11/17/2015	11/17/2015	02/01/2016
AMENDMENT	**PDUFA GOAL**		
N/A	09/17/2016		

NAME & ADDRESS OF APPLICANT: AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19803

Elinore Mercer, Ph.D.
Phone: 858-945-6127
FAX: 301-398-4018
Email: elinore.mercer@astrazeneca.com

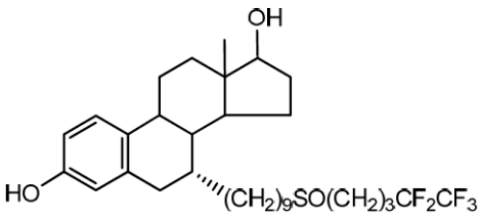
DRUG PRODUCT NAME
Proprietary: Faslodex Injection
Nonproprietary/USAN: Fulvestrant
Code Name#:
Chem. Type:
Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION: treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy

DOSAGE FORM: Solution for Injection
STRENGTH: 250 mg/5 mL

ROUTE OF ADMINISTRATION: Intramuscular Injection
DISPENSED: __X_ Rx ___ OTC
SPECIAL PRODUCTS: ___ Yes _X_ No
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

Chemical Name: 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl)nonyl]estra-1,3,5-(10)-triene-3,17-beta-diol
Molecular Formula: C32H47F5O3S
Molecular Weight: 606.77
CAS Number: [*129453-61-8*]



PROVIDES FOR: Fulvestrant in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following anti-estrogen therapy.

REMARKS/COMMENTS:

The efficacy supplement provides for fulvestrant in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following anti-estrogen therapy. There are no proposed CMC changes in the supplement. Applicant submitted a categorical exclusion request for environmental assessment in accordance with 21 CFR 25.31(b) (estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb). To the best of the knowledge of the applicant, no extraordinary circumstances exist, as referenced in 21 CFR 25.21. The supplement is recommended for approval from CMC standpoint.

CONSULT REVIEW: N/A

COMMENTS/REQUESTS TO BE CONVEYED TO APPLICANT: N/A

CONCLUSIONS & RECOMMENDATIONS:

The supplement is recommended for approval from CMC standpoint.

Zedong Dong -S
Digitally signed by Zedong Dong -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zedong Dong -S, 0.9.2342.19200300.100.1.1=2000341856
Date: 2016.02.02 23:34:09 -05'00'

Zedong Dong, Ph.D.
Quality Assessment Lead (Acting)

Ramesh Raghavachari -S
Digitally signed by Ramesh Raghavachari -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211793, cn=Ramesh Raghavachari -S
Date: 2016.02.03 22:41:15 -05'00'

Ramesh Raghavachari, Ph.D.
Chief, Branch I

cc: Orig. NDA#21-344
HFD-150/Division File
OLDP/DPMA I/ZDong
OLDP/DPMA I/RRaghavachari

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

FDA	21-344 (Labeling Suppl-25 and Efficacy Suppl-26)
Submission Date:	10/28/15, 2/5/2016, 11/17/2015
Brand Name:	Faslodex®
Generic Name:	Fulvestrant injection
Formulation:	50 mg/mL solution for injection
OCP Reviewer:	Jeanne Fourie Zirkelbach, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	AstraZeneca
Submission Type; Code:	NDA 21-344: Suppl-25, SDN 894 (s/n 0100); Suppl-25, SDN 911 (s/n 0105); Suppl-26, SDN 897 (s/n 0099).
Dosing regimen:	500 mg IM injection at intervals of one month with an additional 500 mg dose given two weeks after the initial dose.
Indications:	• Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. • In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

Table of Contents

1 Executive Summary

Faslodex® (fulvestrant) solution for injection is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy, and in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

- The current labeling supplement (Suppl-25; SDN 894) provides the Pregnancy and Lactation Labeling Rule Conversion for the fulvestrant package insert. The Applicant submitted newly conducted simulations (SDN 911) using a population pharmacokinetic model that was previously found acceptable by OCP (NDA 21-344, Suppl-12; SDN 118, 119) in support of the update to Section 8.3 of the package insert. According to the new predictions in the current submission, the fulvestrant concentration reaches 3% and 1.5% of the last steady state trough concentration at the 14th and 17th month from the last injection, respectively. These data were adequate to support the updated labeling to Section 8.3 of the package insert.

- The current efficacy supplement (Suppl-26; SDN 897) was submitted to extend labeling for fulvestrant based on a submitted efficacy supplement for Palbociclib in combination with fulvestrant (NDA 207103; Efficacy Suppl-2, SDN 193) in women with hormone receptor hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following anti-estrogen therapy. The current supplement includes an update to Section 12.3 of the fulvestrant package insert to indicate that there is no drug interaction between palbociclib and fulvestant when these drugs were co-administered (See Clinical Pharmacology Review; NDA 207103; SDN 193 dated 2/5/2016).

Recommendations

The current submissions (Suppl-25 and Suppl-26) are acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 Phase IV Requirements

None.

1.3 Summary of Clinical Pharmacology Findings

Faslodex® (fulvestrant) solution for injection is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen

therapy, and in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative [redacted] (b) (4) Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. The approved dosing regimen is Faslodex 500 mg administered intramuscularly as two concurrent 5 mL injections, on days 1, 15, 29 and once monthly thereafter.

- The current labeling supplement (Suppl-25; SDN 894) provides the Pregnancy and Lactation Labeling Rule Conversion for the fulvestrant package insert. The Applicant submitted the study report for newly conducted simulations using a population pharmacokinetic model that was previously found acceptable by OCP (NDA 21-344, Suppl-12; SDN 118, 119) in support of the update to Section 8.3 of the package insert. According to the new predictions in the current submission, the fulvestrant concentration reaches 3% and 1.5% of the last steady state trough concentration at the 14th and 17th month from the last injection, respectively. These data were adequate to support the updated labeling to Section 8.3 of the package insert.

- The current efficacy supplement (Suppl-26; SDN 897) aims to extend labeling for fulvestrant based on a submitted efficacy supplement for palbociclib in combination with fulvestrant (NDA 207103; Efficacy Suppl-2, SDN 193) in women with hormone receptor hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following anti-estrogen therapy. The current supplement includes an update to Section 12.3 of the fulvestrant package insert to indicate that there is no drug interaction between palbociclib and fulvestant when these drugs were co-administered. This updated labeling language is acceptable, based on the Clinical Pharmacology Review for the palbociclib Efficacy Supplement 2 (See Clinical Pharmacology Review; NDA 207103; Efficacy Suppl-2; SDN 193, DARRTs date: 2/5/2016).

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD
Division of Clinical Pharmacology V

Team Leader: Qi Liu, PhD
Division of Clinical Pharmacology V

Cc: DDOP: CSO - ; MTL - L Amiri Cordestani; MO - S Wedam, Safety MO - A Walker
DCP-5: Reviewers - J Fourie Zirkelbach (CP), (PM) none (PG)
CP TL - Q Liu , PM TL -
DDD - B Booth DD - A Rahman

2 QUESTION BASED REVIEW

2.2 GENERAL CLINICAL PHARMACOLOGY

Pharmacokinetic characteristics of the drug and its major metabolites

2.2.1 What are the single dose and multiple dose pharmacokinetic (PK) parameters?

Previously, the sponsor submitted a two-compartment model with a first order absorption and first order elimination process that was used to fit the fulvestrant concentration-time data from studies 9238IL/0066 and 9238IL/0068. These trials were two randomized, double-blind, parallel-group, multicenter, phase 2 studies to evaluate the efficacy and tolerability of fulvestrant (Faslodex®) 250 mg, 250 mg (plus 250 mg Loading regimen) and 500 mg in Japanese and White postmenopausal women with estrogen receptor positive advanced breast cancer progressing or relapsing after previous endocrine therapy. A summary of the population pharmacokinetic analysis can be found in the previous OCP review (See Clinical Pharmacology Review, NDA 21-344, Suppl-12; SDN 118, 119).

Using the final population PK model described above, a simulation analysis was conducted in the current submission to determine the decline in the plasma fulvestrant concentration after the last steady-state dose. For the simulation, steady-state trough concentrations were assumed to have been achieved after 12 months of dosing, and this is consistent with the fulvestrant PK as summarized in the current package insert. The decline in fulvestrant concentrations was simulated, and the times to achieve target concentrations of 3% and 1.5% of the last steady state Ctrough concentration (after 12 months of dosing at the approved dosing regimen) were determined.

Results from the Current Simulations/Predictions:

The predicted last steady state fulvestrant plasma trough concentration (after 12 months of dosing using the approved dosing regimen) is 13.98 ng/mL (Figure 1 and

- Table 1).

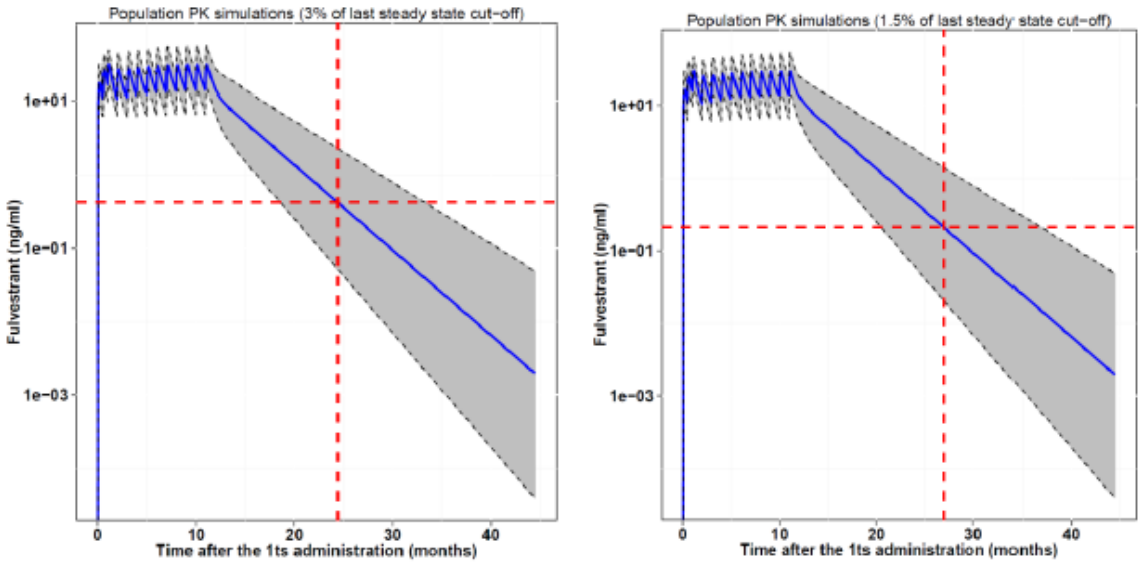
The fulvestrant concentration reaches 3% of the last steady state trough concentration (0.419 ng/mL) at 14 months (population median) after last fulvestrant administration ((Figure 1 and

- Table 1).

The fulvestrant concentration reaches 1.5% of the last steady state trough concentration (0.21 ng/mL) at 17 months (population median) after last fulvestrant administration (Figure 1and

- Table 1).

Figure 1. Simulation of fulvestrant multiple administration (intramuscular administration of 500 mg fulvestrant on Day 1 and Day 15 followed by 500 mg once monthly for 11 months).



Blue line corresponds to the PK exposure level for the median population level. Gray band is the 95% of the population interval. Red dotted lines correspond to the 3% and 1.5% of the last steady state trough concentration, respectively.

Table 1. The summary of the times to achieve the range of target fulvestrant concentrations (3% and 1.5% of last steady state Ctrough) are presented, and include the times for the 50th, 75th, 90th, 97.5th and 100th percentile of patients to achieve concentrations below these specified levels.

Fulvestrant concentration (ng/mL)	% of the last steady state trough concentration	Time after last administration (months)				
		50%	75%	90%	97.5%	100%
13.98*	100	NA	NA	NA	NA	NA
0.419	3	14	16	17	19	28
0.21	1.5	17	19	20	23	33

** 12 months of fulvestrant administration to mimic steady-state*
NA – not applicable

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The **red** text is the applicant proposed acceptable changes to the label.

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNE FOURIE ZIRKELBACH
02/26/2016

QI LIU
02/26/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

OTHER REVIEW(S)

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]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 021344
BLA#</td><td>NDA Supplement #: S- 026
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☒ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: Faslodex Injection
Established/Proper Name: fulvestrant
Dosage Form: Solution for Injection
Strengths: 250 mg/5 mL</td></tr>
<tr><td colspan="3">Applicant: AstraZeneca Pharmaceuticals LP
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: 11-17-15
Date of Receipt: 11-17-15
Date clock started after UN:</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: 9-17-16</td><td>Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: 1-16-16</td><td>Date of Filing Meeting: Virtual 1-20-16</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication/Proposed change: The treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☐ 505(b)(1)
☐ 505(b)(2)
☒ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***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)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): IND 069324	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***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 tracking system.				
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)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		This application according to the sponsor is a "Reverse Parallel Label" Efficacy Supplement coinciding with Palbociclib and Faslodex PLLR supplement. (b) (4) [redacted]

User Fee Status ***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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☒ Not required
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. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulator***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.***

yInformation/Guidances/UCM079320.pdf	☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☐	X	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	X	
• 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)].**	☐	☐	X	
• 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)]?** ***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.***	☐	☐	X	
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**?	☐	☐	☒	

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, 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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***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.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1]	☒	☐	☐	

If not, explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☐	☐	X	In a collaborative data sharing agreement between AZ and Pfizer's

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				sNDA 207103-002.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☐	☒		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&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…"*	☐	☐	☒	N/A as Pfizer conducted the studies under sNDA 207103/002 (IND 069324).
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		PeRC Meeting held 2-10-16.
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	In a collaborative data sharing agreement between AZ and Pfizer's sNDA 207103-002 (IND 069234).
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for***	☐	☐	☒	

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

Review."				
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☐ ☒	☒ ☐	☐ ☐	PLLR was submitted to Supplement 25 and the PLLR information was reviewed simultaneously with Supplement 26 and added to the PI.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request?	☐	☒	☐	PLLR was submitted to Supplement 25 and the PLLR information was reviewed simultaneously with Supplement 26 and

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.				added to the PI.
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☒	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	DPMH
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 8-19-15 ***If yes, distribute minutes before filing meeting***	☒	☐		Preliminary Comments submitted
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

If yes, distribute letter and/or relevant minutes before filing meeting				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1-20-16

BACKGROUND:

Based on a collaborative agreement between the sponsor of Faslodex (fulvestrant) NDA 021344/S-026 and the sponsor of Ibrance (palbociclib), Pfizer submitted NDA 207103/S-002 for (b) (4) AstraZeneca submitted NDA 021344/S-026 for the combination of FASLODEX and IBRANCE (palbociclib) for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following anti-estrogen therapy. Pfizer's NDA 207103/S-002 supplement was approved on 2-19-16. The two supplements are based on the results of Pfizer's PALOMA-3 study.

The collaborative agreement between Pfizer and AstraZeneca provides for consistency between the Full Prescribing Information for both Ibrance (palbociclib) and Faslodex (fulvestrant).

REVIEW TEAM: PLEASE NOTE THIS WAS A VIRTUAL MEETING VIA EMAIL 1-20-16.

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Tilley	
	CPMS/TL:	Alice Kacuba	
Cross-Discipline Team Leader (CDTL)	Laleh Amiri-Kordestani		
Division Director/Deputy	Geoffrey Kim Amna Ibrahim		
Office Director/Deputy			
Clinical	Reviewer:	Efficacy= Suparna Wedam Safety= Amanda Walker	
	TL:	Laleh Amiri-Kordestani	
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Jeanne Fourie-Zirkelbach	
	TL:	Qi Liu	
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Erik Bloomquist	
	TL:	Shenghui Tang	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold	
	TL:	Todd Palmby	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:		
	RBPM:		
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	EA Reviewer: Zedong Dong TL: Ramesh Raghavachari		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Morgan Walker	
	TL:	Sharon Mills	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nicholas Senior	
	TL:	Jessica Cleck-Derenick	
OSE/DMEPA (proprietary name,	Reviewer:		

carton/container labels)			
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DPMH	Reviewer:	Miriam Dinatale	
	TL:	Tamara Johnson	
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues:	☒ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
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):	

• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Geoffrey Kim, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTION ITEMS

☒	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).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY R TILLEY
03/01/2016

ALICE KACUBA
03/01/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: February 29, 2016 **Date Consulted:** January 29, 2016

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 1 (DOP1)

Drug: Faslodex (fulvestrant) Injection

Proposed Indication: In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

NDA: 21344/S-026

Applicant: AstraZeneca Pharmaceuticals LP

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- DPMH consult request dated January 29, 2016, DARRTS Reference ID 3843329
- Applicant's submitted background package for NDA 21344, Faslodex (fulvestrant)

- DPMH Review of Faslodex (fulvestrant), NDA 21344/S-025. M. Dinatale, D.O. February 9, 2016. DARRTS Reference ID 3883217

Consult Question:
DOP1 requests that DPMH "assist in revising the Faslodex S-026 PI into the PLLR format conversion."

INTRODUCTION
On November 17, 2015, AstraZeneca Pharmaceuticals LP submitted a 505(b)(1) new drug application (NDA) for an efficacy supplement for Faslodex (fulvestrant) Injection, NDA 21344/S-026. In addition to the current indication, AstraZeneca has added a proposed indication to use Faslodex in combination with palbociclib (Ibrance) for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

Faslodex was originally approved on April 25, 2002 for treatment of estrogen receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

The Division of Oncology Products 1 (DOP1) consulted the Division of Pediatric and Maternal Health (DPMH) on January 29, 2016 to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements.

BACKGROUND
Pregnancy and Breast Cancer
Breast cancer occurs in 1 in every 3,000 pregnant woman and is the most common type of cancer found during pregnancy, while breastfeeding and in the first year after delivery.[1]

Fulvestrant and Drug Characteristics
Fulvestrant is an estrogen receptor antagonist that competitively binds to the estrogen receptor and down-regulates the estrogen receptor protein in human breast cancer cells. Fulvestrant has a molecular weight of 606.77 Daltons, is 99% plasma-protein bound and has a half-life of 40 days.

Pregnancy and Lactation Labeling
On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[2] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products

[1] http://www.cancer.org/cancer/breastcancer/moreinformation/pregnancy-and-breast-cancer. Accessed 12/28/2015.
[2] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[3] format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

DISCUSSION OF PREGNANCY AND LACTATION LABELING RECOMMENDATIONS

In February 2016, DPMH conducted a review of published literature regarding fulvestrant and pregnancy, lactation and females and males of reproductive potential, and provided labeling recommendations for this application to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The reader is referred to the DPMH review by M. Dinatale, D.O., for further details.[4]

CONCLUSIONS

DPMH has the following recommendations for Faslodex (fulvestrant) labeling:

- **Warnings and Precautions, Section 5.3**
  - Based on the increased likelihood of adverse fetal and infant effects due to the fulvestrant's mechanism of action and embryofetal toxicity seen in animal reproduction studies with fulvestrant, a subsection describing embryo- and/or fetal risks ("Embryofetal Toxicity") as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4)).
- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of fulvestrant labeling was structured in the PLLR format to include the "Risk Summary" and "Data" subsections.[5]
- **Lactation, Section 8.2**
  - The "Lactation" subsection of fulvestrant labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections.[6]
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" subsection fulvestrant labeling was formatted in the PLLR format to include the "Pregnancy Testing," "Contraception," and "Infertility" subsections to advise females of reproductive potential to get pregnancy testing prior to starting fulvestrant, to use effective contraception during treatment with fulvestrant because of the potential for adverse

[3] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

[4] DPMH Review of Faslodex (fulvestrant), NDA 21344/S-025. M. Dinatale, D.O. February xx, 2016. DARRTS Reference ID 3883217

[5] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[6] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

fetal and infant effects from maternal exposure and to advise females and males of reproductive potential of the risk of infertility with use of fulvestrant.[7]

- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of fulvestrant labeling was updated to correspond with changes made to sections 5.3, 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS

DPMH revised subsections 5.3, 8.1, 8.2, 8.3 and 17 of Faslodex (fulvestrant) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling.)

DPMH Proposed Labeling for Faslodex (fulvestrant) Injection

(b) (4)

[redacted]

[7] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

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/s/

MIRIAM C DINATALE
02/29/2016

TAMARA N JOHNSON
02/29/2016

LYNNE P YAO
02/29/2016

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:	February 26, 2016
To:	Geoffrey Kim, MD 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)**
	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Nicholas Senior, PharmD, JD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FASLODEX (fulvestrant)
Dosage Form and Route:	injection
Application Type/Number/Supplement Number:	NDA 021344/S-026
Applicant:	AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On November 17, 2015, AztraZeneca submitted for the Agency's review an efficacy supplement to their approved New Drug Application (NDA) 021344/S-026 for FASLODEX (fulvestrant) injection. In this efficacy supplement, the Applicant seeks a labeling extension for FASLODEX (fulvestrant) on the basis of Study A541023 (also known as PALOMA-3). The proposed indication is as follows: for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER-2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

FASLODEX was approved on April 25, 2002 and is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

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 (DOP1) on January 29, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for FASLODEX (fulvestrant) injection.

2 MATERIAL REVIEWED

- Draft FASLODEX (fulvestrant) injection PPI received on November 17, 2015, and received by DMPP and OPDP on February 22, 2016.
- Draft FASLODEX (fulvestrant) injection Prescribing Information (PI) received on November 17, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 22, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade 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 have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- 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
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

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.

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/s/

MORGAN A WALKER
02/26/2016

NICHOLAS J SENIOR
02/26/2016

SHARON R MILLS
02/26/2016

LASHAWN M GRIFFITHS
02/26/2016

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: Februrary 16, 2016

To: Amy Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on NDAs 207103; 021344
IBRANCE (palbociclib) capsules, for oral use
FASLODEX (fulvestrant) injection

OPDP has reviewed the proposed product labeling (PIs) for IBRANCE (palbociclib) capsules, for oral use and FASLODEX (fulvestrant) injection as requested in the consults dated November 13, 2015, and January 29, 2016, respectively. The following comments, using the proposed substantially complete, marked-up version of the PIs emailed to OPDP by Amy Tilley on February 2, 2016, are provided below. Specifically, OPDP has reviewed the HIGHLIGHTS OF PRESCRIBING INFORMATION, along with Sections 1, (INDICATIONS AND USAGE), 2 (DOSAGE AND ADMINISTRATION), 5 (WARNINGS AND PRECAUTIONS), 6 (ADVERSE REACTIONS), 8 (USE IN SPECIFIC POPULATIONS), 13 (NONCLINICAL TOXICOLOGY), and 14 (CLINICAL STUDIES) of both labels.

Please note that comments on the proposed Opdivo patient labeling will be provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs.

Ibrance:

- Clinical Studies: Please consider adding the 95% confidence intervals for the overall response rate and duration of response, as this gives a fuller pictures of the actual patient response to Ibrance therapy.

Faslodex:

- Overall: Please consider updating the Fulvestrant label to be consistent with all accepted changes to the Ibrance label.
- Clinical Studies:
  - We recommend the deletion of this section as the updated information renders this information irrelevant and unnecessary.
  - (b) (4)

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NICHOLAS J SENIOR
02/16/2016

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 021344/S-026

Application Type: Efficacy Supplement

Drug Name/Dosage Form: Faslodex Injection (fulvestrant) Solution for Injection

Applicant: AstraZeneca Pharmaceuticals LP

Receipt Date: November 17, 2015

Goal Date: 9-16-16

1. Regulatory History and Applicant's Main Proposals

NDA 021344 was approved on April 25, 2002. In the sNDA Preliminary Comments dated August 19, 2015, several agreements were made regarding this sNDA. AstraZeneca would refer to Pfizer's Study A5481023 PALOMA-3 conducted under Pfizer's IND 069324. PALOMA-3 was conducted by Pfizer in collaboration with AstraZeneca. Pfizer's sNDA 207103/002 for the combination of Faslodex and Ibrance (palbociclib) for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following anti-estrogen therapy was submitted on October 14, 2015.

In the August 19, 2015 sNDA Preliminary Comments, it was agreed that AstraZeneca would submit a reverse parallel labeling extension for fulvestrant on the basis of PALOMA-3 to ensure consistency across the labeling for fulvestrant and palbociclib. Based on the collaborative agreement between the two sponsors, AstraZeneca is cross-referencing the data supporting the Palbociclib PALOMA-3 sNDA 207103/002, to support a parallel review for both the Faslodex and Ibrance product inserts. Also, as agreed to in the August 19, 2015, sNDA Preliminary Comments, this sNDA submission would be submitted within 60 days of the Palbociclib sNDA submission to support a near simultaneous review and updates to both product inserts.

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

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 9, 2016. The resubmitted PI will be used for further labeling review.

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

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

"**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

YES 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:

YES 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:

YES 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:

Adverse Reactions in Highlights

NO

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: (b) (4) [redacted]

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:

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:

N/A 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:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 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.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
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
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 (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *The PI is not in PLLR format.*

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:

YES 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:

YES 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:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 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:

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.

----------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*

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

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/s/

AMY R TILLEY
01/28/2016

ALICE KACUBA
01/28/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s026

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021344 SUPPL # 026 HFD # 150

Trade Name Faslodex® Solution for Injection

Generic Name fulvestrant

Applicant Name AstraZeneca Pharmaceuticals LP

Approval Date, If Known 3-2-16

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021344

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 PALOMA-3 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Ibrance (palbociclib) 207103/S-002

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 069234 YES ☐ ! NO ☒
! Explain: Collaborative Agreement between sponsor of IND 069324 and NDA 207103/S-002 (Pfizer) and NDA 021344/S-026 (AstraZeneca).

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain: Study PALOMA-3 was conducted by Pfizer. Both sponsors have a collaborative data sharing agreement [redacted] (b) (4) Now both Full Prescribing Information is consistent between both product labels.

==========

Name of person completing form: Amy Tilley
Title: Regulatory Project Manager
Date: February 23, 2016

Name of Office/Division Director signing form: Geoffrey Kim, MD
Title: Division Director, DOP1

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY R TILLEY
03/07/2016

GEOFFREY S KIM
03/07/2016

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission.*

Definitions:

Deferral *– A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.*

Full Waiver *– On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information MUST be included in the pediatric use section of labeling.*

Partial Waiver *– FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.*

Pediatric Assessment *– The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.*

Pediatric Plan *– A pediatric plan is the applicant's statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient- *21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page *– The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☒ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: sNDA 021344/26

PRODUCT PROPRIETARY NAME: Faslodex Injection **ESTABLISHED/GENERIC NAME: Fulvestrant**

APPLICANT/SPONSOR: AstraZeneca Pharmaceuticals LP

PREVIOUSLY APPROVED INDICATION/S:
(1) Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
(1) In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative (b) (4)
(2) _____
(3) _____
(4) _____

sNDA STAMP DATE: November 17, 2015

PDUFA GOAL DATE: **Targeted Action date of 2-29-16** due to the reverse parallel labeling extension for fulvestrant on the basis of PALOMA-3 Study to ensure consistency across the labeling for fulvestrant and palbociclib. The division would like to do a "near simultaneous" review of Faslodex with Palbociclib sNDA 207103/2 and thus the Targeted Action date of 2-29-16.

SUPPLEMENT TYPE: Efficacy Supplement SE1

SUPPLEMENT NUMBER: 026

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☐ No ☒ Based on collaborative agreement between Pfizer and AstraZeneca and agreement from the FDA, AstraZeneca is cross-referencing to the Pfizer PSP included in NDA 20-7103, Module 1, Section 1.9.1. Reference is made to AstraZeneca's June 12, 2015, request for a Type B meeting with DOP1, the meeting package was submitted July 13, 2015, and our Division's preliminary comments dated August 19, 2015 in which agreements regarding this sNDA were made. As agreed to in our August 19, 2015, Type B meeting preliminary comments, AstraZeneca is seeking a reverse parallel labeling extension for fulvestrant on the basis of PALOMA-3 Study to ensure consistency across the labeling for fulvestrant and palbociclib.

In an email from George Greeley dated January 28, 2016 he stated: We will agree with the plan by the Division to allow Faslodex to reference Pfizer's Agreed iPSP for NDA 207103 Ibrance (palbociclib). This product was reviewed at PeRC on 1/20/15. This supplement will still require a review by the PeRC prior to approval. Please submit a request to have this product scheduled for review for any Wednesday in February and also note that the Division will not need to attend in-person for this breast cancer indication.

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☐ No ☐ N/A (see above)

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR #_____ NDA #_____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1 Pediatric age group(s) to be waived.

2 Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3 Provide justification for Waiver: Disease/condition does not exist in children.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language: N/A

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY R TILLEY
02/05/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 021344 BLA #	NDA Supplement # 026 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Faslodex Injection Established/Proper Name: Fulvestrant Dosage Form: Solution for Injection		Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable):
RPM: Amy Tilley		Division: DOP1

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 17, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☒ Not applicable

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 1-28-16 DMEPA: ☒ None DMPP/PLT (DRISK): ☒ 2-26-16 OPDP: ☒ 2-16-16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Virtual Filing Meeting 1-20-16 Review Date: 3-1-16 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 2-10-16 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg Sponsor cancelled mtg after receiving the Preliminary Comments dated 8-19-15.
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ 3-1-16
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	2-19-16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Included in Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ See Clinical Review
Statistical Review(s) *(indicate date for each review)*	☒ See Clinical Review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ See Clin Pharm Review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 2-26-16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ 2-29-16
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	EA Review: 2-2-16
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable Re-evaluation date: ☐ Withhold recommendation ☒ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

AMY R TILLEY
03/07/2016

ALICE KACUBA
03/07/2016

From: Mercer, Elinore
To: Tilley, Amy
Cc: Lowry, Helen
Subject: Re: URGENT sNDA 21344-26 Faslodex - FDA Revised PPI
Date: Wednesday, March 02, 2016 12:29:39 PM

Hi Amy,
That's correct. We accepted your changes in the PPI, made no changes to the PI, and ensured correct formatting in the PPI.

Many thanks!
Elinore

Sent from my iPhone

On Mar 2, 2016, at 12:21 PM, Tilley, Amy <Amy.Tilley@fda.hhs.gov> wrote:

> Elinore, just to make sure you basically accepted all our changes in the PPI and fixed the formatting of the second bullet in the What is Faslodex paragraph correct?
>
> Also, please confirm you have made no other revisions to the **PI** as your email below states "Please find attached our revised **PI**-PPI."
>
> Thank you in advance for your prompt response.
> *Amy*
>
> ---
>
> **From:** Mercer, Elinore [mailto:elinore.mercer@astrazeneca.com]
> **Sent:** Wednesday, March 02, 2016 11:55 AM
> **To:** Tilley, Amy
> **Cc:** Lowry, Helen
> **Subject:** RE: URGENT sNDA 21344-26 Faslodex - FDA Revised PPI
>
> Dear Amy,
>
> Please find attached our revised PI-PPI. We have incorporated the Agency's suggested changes.
>
> We have scheduled the formal submission to occur by COB today.
>
> Many thanks, Amy!
>
> Kind regards,
> Elinore
>
> **Elinore M. Mercer, Ph.D., R.A.C.**
> Director, Regulatory Affairs, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
(858) 945-6127
elinore.mercer@astrazeneca.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Wednesday, March 02, 2016 10:08 AM
To: Mercer, Elinore <elinore.mercer@astrazeneca.com>
Cc: Lowry, Helen <Helen.Lowry1@astrazeneca.com>
Subject: URGENT sNDA 21344-26 Faslodex - FDA Revised PPI
Importance: High

Elinore,

Attached is the FDA Revised PPI for your review. Please respond **by Noon today, March 2, 2016.** As always, follow up with an official submission to the NDA.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

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/s/

AMY R TILLEY
03/02/2016

From:	Tilley, Amy
To:	elinore.mercer@astrazeneca.com
Cc:	Lowry, Helen (Helen.Lowry1@astrazeneca.com)
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	URGENT sNDA 21344-26 Faslodex - FDA Revised PPI
Date:	Wednesday, March 02, 2016 10:07:43 AM
Attachments:	FDA Revised PPI 3-2-16.doc
Importance:	High

Elinore,

Attached is the FDA Revised PPI for your review. Please respond **by Noon today, March 2, 2016.** As always, follow up with an official submission to the NDA.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
03/02/2016

From:	Tilley, Amy
To:	"elinore.mercer@astrazeneca.com"
Cc:	"Lowry, Helen (Helen.Lowry1@astrazeneca.com)"
Bcc:	Amiri Kordestani, Laleh (FDA); Walker, Morgan
Subject:	Addt to PPI URGENT sNDA 21344/26 Faslodex - FDA Revised PI-PPI
Date:	Tuesday, March 01, 2016 3:36:15 PM
Importance:	High

Elinore, after our telephone conversation regarding your possible revisions to the PPI we have the following comments for your consideration prior to responding to my email below.

The FDA concurs with the term "(metastatic)" being added to the "What is FASLODEX?" section of the PPI.

(b) (4)

Kindly confirm receipt of this email.

Regards.

Amy

From: Tilley, Amy
Sent: Tuesday, March 01, 2016 12:43 PM
To: 'elinore.mercer@astrazeneca.com'
Cc: Lowry, Helen (Helen.Lowry1@astrazeneca.com)
Subject: URGENT sNDA 21344/26 Faslodex - FDA Revised PI-PPI
Importance: High

Elinore,

Please see the attached FDA Revised PI-PPI which we request your **emailed response to by 2 pm today.** As always, follow up with an official submission to the NDA.

Our only revisions to the PI were the revision of the dates at the end of Highlights and Recent Major Changes.

Please also see our revisions to the PPI which also includes a revised date at the end of the PPI.

Please confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1,

CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
03/01/2016

From:	Tilley, Amy
To:	"elinore.mercer@astrazeneca.com"
Cc:	Lowry, Helen (Helen.Lowry1@astrazeneca.com)
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	URGENT sNDA 21344/26 Faslodex - FDA Revised PI-PPI
Date:	Tuesday, March 01, 2016 12:43:12 PM
Attachments:	FDA revised PI-PPI - 3-1-16.doc
Importance:	High

Elinore,

Please see the attached FDA Revised PI-PPI which we request your **emailed response to by 2 pm today.** As always, follow up with an official submission to the NDA.

Our only revisions to the PI were the revision of the dates at the end of Highlights and Recent Major Changes.

Please also see our revisions to the PPI which also includes a revised date at the end of the PPI.

Please confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
03/01/2016

From:	Tilley, Amy
To:	"Mercer, Elinore"
Cc:	Lowry, Helen
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	RE: TIME SENSITIVE sNDA 21344-S-26 Faslodex - Agreed upon label
Date:	Tuesday, March 01, 2016 10:23:06 AM

Elinore, we agree with your revision below regarding the faslodex label. However, we have updated the revision dates to 03/2016 as we anticipate an upcoming action.

Do you concur with the updates to the revision dates to 03/2016?

Regards.

Amy

From: Mercer, Elinore [mailto:elinore.mercer@astrazeneca.com]
Sent: Monday, February 29, 2016 9:37 AM
To: Tilley, Amy
Cc: Lowry, Helen
Subject: RE: TIME SENSITIVE sNDA 21344-S-26 Faslodex - FDA Revised Label

Hi Amy,
Please find attached our updated draft of the Faslodex label for S-026.

Regarding FDA's proposed change [redacted] (b) (4) However, AstraZeneca recognizes the imposition by FDA to provide consistency in this language between the FASLODEX and palbociclib labels, and as such, we have incorporated this change into the FASLODEX label.

Also, regarding FDA's proposed change in Section 14, AstraZeneca understands the Agency's desire to maintain consistency with the IBRANCE label. As such, AstraZeneca proposes to include the following as a subheading as in the IBRANCE label: "**Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy."**

This label will be formally submitted tomorrow, March 1, 2016.

We look forward to receiving response from the Agency, and as always, please don't hesitate to reach out with any questions or concerns.

Kind regards,
Elinore

Elinore M. Mercer, Ph.D., R.A.C.
Director, Regulatory Affairs, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
(858) 945-6127
elinore.mercer@astrazeneca.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Friday, February 26, 2016 11:47 AM
To: Mercer, Elinore <elinore.mercer@astrazeneca.com>
Subject: TIME SENSITIVE sNDA 21344-S-26 Faslodex - FDA Revised Label
Importance: High

Elinore,

Attached is the FDA revised Faslodex label for Supplement 26. Please merge this label with the finalized label from Supplement 25 and respond by email **no later than 10 am on Monday, Feb 29, 2016.**
As always please follow up with an official submission to the NDA.

Kindly confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
03/01/2016

From: Tilley, Amy
To: elinore.mercer@astrazeneca.com
Cc: Lowry, Helen (Helen.Lowry1@astrazeneca.com)
Subject: Quick question re Faslodex 26 - Need financial disclosure forms FDA 3454 and/or 3455
Date: Monday, February 29, 2016 11:46:08 AM
Importance: High

Elinore,

I do not see any financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) that were submitted for Faslodex S-26.

As discussed, please email me and officially submit asap a cover letter stating the financial disclosure forms were referenced to NDA 207103 along with a completed and signed 356h form.

Thanks.

Amy

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/s/

AMY R TILLEY
02/29/2016

From:	Tilley, Amy
To:	"elinore.mercer@astrazeneca.com"
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE sNDA 21344-S-26 Faslodex - FDA Revised Label
Date:	Friday, February 26, 2016 11:47:15 AM
Attachments:	FDA revised Faslodex label S-26 - 2-26-16.doc
Importance:	High

Elinore,

Attached is the FDA revised Faslodex label for Supplement 26. Please merge this label with the finalized label from Supplement 25 and respond by email **no later than 10 am on Monday, Feb 29, 2016.**

As always please follow up with an official submission to the NDA.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993

☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
02/26/2016

PeRC Meeting Minutes
February 10, 2016

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Linda Lewis
Ikram Elayan
Thomas Smith
Daiva Shetty
Meshaun Payne
Dianne Murphy
Gerri Baer
Rosemary Addy (Dysport and KamRab reviews only)
Wiley Chambers (Did not review Afluria)
Julia Pinto
Maura O'Leary
Lili Mulugeta
Freda Cooner
Peter Starke
Gil Burckart
Raquel Tapia
Greg Reaman
Dionna Green
Lisa Faulcon (KamRab review only)
Adrienne Hornatko-Munoz (KamRab, Afluria and Flucelvax reviews only)
Barbara Buch
Rachel Witten
Michelle Roth-Kline
George Greeley

Agenda

(b) (4)

9:20	IND 13333/31	KamRAB (Rabies immune globulin (human)) iPSP (b) (4) Deferral	CBER /OBRR	Jiahua Qian	(b) (4)
9:35	BLA 125408/127 & 125408/101	Flucelvax Quadrivalent /Trivalent Partial Waiver/Assessment/ Deferral/Plan/PREA PMR Change (w/Agreed iPSP)	CBER/ OVRR	Helen Gemignani	Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and types B contained in the vaccine
9:50	BLA 125254/565	Afluria Quadrivalent influenza vaccine Partial Waiver/Deferral/Plan	CBER/ OVRR	Timothy Fritz	Prevention of influenza disease caused by influenza A subtype viruses and type B viruses present in the vaccine

(b) (4)

(b) (4)

11:20	BLA 761033	Cinqair (reslizumab) Partial Waiver/Assessment (w/agreed iPSP)	DPARP	Colette Jackson	For add-on maintenance treatment of patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
11:30	NDA 208215	Descovy (emtricitabine/tenofovir alafenamide) FDC tablets Partial Waiver/Deferral/Plan/Assessment (w/Agreed iPSP)	DAVP	Myung-Joo (Patricia) Hong	For use in combination with antiretrovirals for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
11:40	IND 125589	GS-9883/F/TAF FDC Tablets iPSP Partial Waiver/Assessment	DAVP	Suzanne Strayhorn	Treatment of HIV
	NDA 21344/026	Faslodex (fulvestrant) Solution for injection (Full Waiver)	DOP1	Amy Tilley	In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)

(b) (4)

(b) (4)

(b) (4)

KamRAB (Rabies immune globulin (human)) iPSP (b) (4) Deferral

- Proposed Indication: (b) (4)
- The division clarified this product would be used in any rabies-exposed patients in conjunction with rabies vaccine. Therefore, the PeRC recommended that pediatric clinical trial enrollment be opened to ANY patient who is exposed, regardless of age. (b) (4)
- *PeRC Recommendations:*

- The PeRC recommended that the currently planned pediatric trial be opened to enrollment to any pediatric patient who is exposed to rabies. (b) (4) The PeRC recommended that the Division suggest to the sponsor that they request a deferral of studies for the entire pediatric age range. The PeRC recommended that the sponsor submit a study protocol now and begin pediatric studies at the earliest time possible and that the protocol should be submitted prior to submission of the BLA. PeRC advised the Division that the sponsor could be advised (b) (4)
- See comments in the iPSP sent to the Division on February 10, 2016.

Flucelvax Partial Waiver/Assessment/Deferral/Plan/PREA PMR Change (w/Agreed iPSP)

- Indication: Active immunization for the prevention of influenza disease caused by influenza subtypes A and type B contained in the vaccine.
- The current studies were submitted in response to a PREA requirement and the data contained in this application fulfill PREA for children and adolescents 4-17 years of age. However, because there is a new dosing regimen (for children 4 to< 8 years of age undergoing initial vaccination – receive 2 doses) this application also triggers PREA as a new dosing regimen.
- The PDUFA goal date for Flucelvax (TIV) is July 22, 2016.
- The division clarified that a BLA for the sponsor's quadrivalent vaccine Flucelvax QIV(see below) is currently under review.
- The sponsor is expecting to use the results of their PREA-required TIV dose-finding study in children 6 months to < 4 months to formulate Flucelvax QIV for this age group. The sponsor will conduct a pediatric study in this age group using the Flucelvax QIV product. The results from this Flucelvax QIV study will fulfill both the Flucelvax TIV and Flucelvax QIV assessments for infants and children 6 months to 4 years of age (see below).
- The division also explained that another PREA PMR for Flucelvax (TIV) for the age group 6 months to <4 years of age will be released and a new PMR will be issued and fulfilled with the planned Flucelvax QIV study.
- *PeRC Recommendations*:
  - The PeRC agreed with the Division to waive studies in infants less than 6 months of age as the product does not represent a meaningful therapeutic benefit over initiating vaccination at 6 months of age and is not likely to be used in this age group and agreed with a deferral in infants and children 6 months to 4 years of age.
  - The PeRC recommended that the sponsor be encouraged to advance their timeline for the deferred study of Flucelvax QIV in children 6 months to < 4 years to an earlier flu season or provide rationale for the 2019 start date.

Flucelvax Quadrivalent Partial Waiver/Assessment/Deferral/Plan/ (w/Agreed iPSP)

- Proposed Indication: Active immunization for the prevention of influenza disease caused by influenza subtypes A and types B contained in the vaccine.
- This application is subject to PREA because of a new active ingredient. The data contained in this supplemental application will fulfill PREA for children and adolescents 4-17 years of age.
- The PDUFA goal date for Flucelvax Quadrivalent (QIV) is May 23, 2016.
- The sponsor is expecting to use the results of the ongoing Flucelvax (TIV) dose-finding study in children 6 months to <4 years to formulate Flucelvax QIV for children in this age group. The results from a deferred Flucelvax QIV study will fulfill both the Flucelvax TIV and QIV assessments in infants and children 6 months to 4 years of age.
- *PeRC Recommendations*:
    - The PeRC agreed with the Division to waive studies in infants less than 6 months of age as the product does not represent a meaningful therapeutic benefit over initiating vaccination a 6 months of age and is not likely to be used in this age group, and agreed with a deferral in infants and children 6 months to 4 years of age.
    - The PeRC recommended that the sponsor be encouraged to advance their timeline for the deferred study of Flucelvax QIV in children 6 months to <4 years to an earlier flu season or provide rationale for the 2019 start date.

Afluria Quadrivalent influenza vaccine Partial Waiver/Deferral/Plan

- Approved Indication: Prevention of influenza disease due to influenza virus subtypes A and B present in the vaccine
- Proposed Indication: Prevention of influenza disease caused by influenza A subtype viruses and type B viruses present in the vaccine
- The product triggers PREA as a new active ingredient. (see discussion above).
- PDUFA Goal date of August 26, 2016.
- The Division clarified that the pediatric studies associated with the original BLA approval were deferred PREA studies and were submitted in an efficacy supplement supporting licensure in children 6 months and older in September 2009. Due to previous reports of febrile seizures and events predominantly in children <5 years following administration of a Southern Hemisphere 2010 formulation, the clinical studies are grouped by age cohort to allow evaluation of safety in older pediatric age groups first.
- *PeRC Recommendations:*
    - The PeRC agreed with the Division to waive studies in pediatric patients less than 6 months of age as the product fails to represent a meaningful therapeutic benefit over existing therapies and a deferral in patients 6 months to 17 years of age.

(b) (4)

[redacted]

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(b) (4)

Cinqair (reslizumab) Partial Waiver/Assessment (w/agreed iPSP)

- Proposed Indication: An interleukin 5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
- The product triggers PREA as a new active ingredient and has a PDUFA Goal date of March 28, 2016.
- The division clarified that this product is administered as an IV injection (b) (4) This product was recently reviewed at a Pulmonary-Allergy Drugs Advisory Committee meeting. The division noted concerns regarding the lack of efficacy of the product in patients 12-17 years of age. The AC voted 14-0 against approval of this IV product. (b) (4)
- (b) (4)
- *PeRC Recommendations:*
  - The PeRC agreed with the Division's plan to waive studies of the IV formulation patients less than 12 years of age because the product would be ineffective and also agreed that the assessment in patients 12 to 17 years of age as studies is complete. (b) (4)

Descovy (emtricitabine/tenofovir alafenamide) FDC tablets Partial Waiver/Deferral/Plan/Assessment (w/Agreed iPSP)

- Proposed Indication: For use in combination with antiretrovirals for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older with antiretroviral treatment history or who are virologically suppressed to replace their

current antiretroviral treatment regimen

- The product triggers PREA as a new active ingredient and has a PDUFA Goal date of April 7, 2016.

- The Division noted that this fixed dose combination product application is based on bioavailability and bioequivalence data only. There were no clinical trials included in this application.
- The iPSP includes plans for studies down to 4 weeks of age. The division agrees with this plan because this combination product (2 NRTI's) is part of the preferred backbone of therapy for HIV patients down to 1 month of age.
- *PeRC Recommendations:*
  - The PeRC agreed to the Division's plan for partial waiver in patients less than 4 weeks of age as studies are impossible and highly impractical and to a deferral in patients 4 weeks to less than 12 years old.

  - The PeRC agreed to the assessment in patients 12-18 years of age.

GS-9883/Emtricitabine/Tenofovir Alafenamide FDC Tablets iPSP Partial Waiver/Deferral

- Proposed Indication: Treatment of HIV
- The Division clarified that this fixed dose combination product includes INSTI (GS-9883) plus 2 NRTIs (emtricitabine and tenofovir alafenamide). This regimen is likely to be used in patients down to 1 month of age because INSTI treatment may be an alternative to PI and may, ultimately be safer than treatment with PI. Therefore, the division is requiring that the sponsor develop a formulation that could be used down to 1 month of age because use of a single FDC would be of potential benefit.
- The plan includes patients who are treatment naïve up to 6 months of age. The division disagrees with this approach because this population is increasingly difficult to enroll. Therefore the division is recommending that treatment naïve patients up to 2 years of age may be enrolled as well as patients who are not treatment naïve but are virologically suppressed.
- The division will require the sponsor to attempt to develop a formulation; however, currently it is premature to establish the type of formulation because it is still not clear what to dose of the individual components will be down to 1 months of age for TAF and for GS-9883.
- *PeRC Recommendations:*
  - The PeRC agreed with the sponsor's plan to request a partial waiver in pediatric patients 0 to less than 4 weeks as studies are impossible or highly impracticable and to the deferral in patients 1 month to 17 years.
  - The PeRC agreed to the Divisions comments provided in the iPSP

Faslodex (fulvestrant) Solution for injection (Full Waiver)

- Previously Approved Indication: Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

- Proposed Indication: In combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (b) (4)
- The product triggers PREA as a new indication and has a PDUFA date of August 27, 2016.
- *PeRC Recommendations:*
    - The PeRC agreed with the Division's plan for a full waiver of pediatric studies as studies are impossible or highly impractical.

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/s/

MESHAUN L PAYNE
02/26/2016

From:	Tilley, Amy
To:	"Mercer, Elinore"
Cc:	"Lowry, Helen"
Subject:	RE: TIME SENSITIVE sNDA 21344/26 Faslodex - FDA revised PI
Date:	Monday, February 22, 2016 9:32:57 AM
Importance:	High

Elinore, please note we always need the annotated label in Word format.

Please email me the annotated label in Word format asap and also officially submit the Word version to the NDA.

Please confirm receipt of this email.

Regards.

Amy

From: Tilley, Amy
Sent: Monday, February 22, 2016 9:31 AM
To: 'Mercer, Elinore'
Cc: Lowry, Helen
Subject: RE: TIME SENSITIVE sNDA 21344/26 Faslodex - FDA revised PI

Thank you and I am in receipt of this email.

Amy

From: Mercer, Elinore [mailto:elinore.mercer@astrazeneca.com]
Sent: Sunday, February 21, 2016 11:59 AM
To: Tilley, Amy
Cc: Lowry, Helen
Subject: RE: TIME SENSITIVE sNDA 21344/26 Faslodex - FDA revised PI

Dear Amy,
I hope you had a nice weekend! Please find attached AstraZeneca's revised USPI for the Agency's review.

As requested, AstraZeneca has accepted all the changes in the USPI proposed by the FDA except where annotated with track changes. AstraZeneca has suggested several changes throughout the label, including in Sections 6.1 and 14, to provide greater clarity and accuracy for prescribers and patients.

Reference is made to the Prior Approval Efficacy Supplement (Sequence No. 0100/Supplement No. 25), submitted on October 28, 2015, and to the email sent from Ms. Charlene Wheeler to Elinore Mercer on February 19, 2016. Label negotiations regarding [redacted] (b) (4) and the Patient Information are ongoing for Supplement No. 25.

Please confirm receipt of this email, and please don't hesitate to reach out with any questions or concerns.

Kind regards,
Elinore

Elinore M. Mercer, Ph.D., R.A.C.
Director, Regulatory Affairs, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
(858) 945-6127
elinore.mercer@astrazeneca.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, February 18, 2016 2:13 PM
To: Mercer, Elinore <elinore.mercer@astrazeneca.com>
Subject: TIME SENSITIVE sNDA 21344/26 Faslodex - FDA revised PI
Importance: High

Elinore,

Attached is the FDA revised PI for Faslodex for your review. Please respond **by 9 am Monday, February 22, 2016.**

Please confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

---

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/s/

AMY R TILLEY
02/22/2016

From:	Tilley, Amy
To:	"elinore.mercer@astrazeneca.com"
Bcc:	Amiri Kordestani, Laleh (FDA)
Subject:	TIME SENSITIVE sNDA 21344/26 Faslodex - FDA revised PI
Date:	Thursday, February 18, 2016 2:13:24 PM
Attachments:	sNDA 21344 26 - FDA revd PI-PPI 2-18-16.doc
Importance:	High

Elinore,

Attached is the FDA revised PI for Faslodex for your review. Please respond **by 9 am Monday, February 22, 2016.**

Please confirm receipt of this email.

Regards.
Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone)● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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

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/s/

AMY R TILLEY
02/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**
Requesting same Reviewers as Palbociclib sNDA 207103/002
Morgan Walker / Barbara Fuller

FROM: (Name/Title, Office/Division/Phone number of requestor)
Amy Tilley/RPM/OHOP/DOP1/301-796-3994

REQUEST DATE: 1-29-16

NDA/BLA NO.: sNDA 21344/026

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG: Faslodex (fulvestrant)

PRIORITY CONSIDERATION: Priority

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
Since a "near simultaneous" review is being done with Palbociclib the request date is the same as sNDA 207103/002.

SPONSOR:
AstraZeneca Pharmaceuticals LP

PDUFA Date: **Target Date: 2-29-16**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION – Additional Indication

EDR link to submission: **\\CDSESUB1\evsprod\NDA021344\021344.enx**

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: DOP1 requests PLT to review the PPI regarding Faslodex (fulvestrant) sNDA 21344-026 Efficacy Supplement.

Filing/Planning Meeting: Virtual Meeting 1-20-16

Mid-Cycle Meeting: Virtual Meeting 1-20-16

Labeling Meetings: February 2, 16, and 18, 2016 – combined with Palbociclib label meetings

Wrap-Up Meeting: N/A

SIGNATURE OF REQUESTER
Amy Tilley *{See appended electronic signature page}*

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☒ eMAIL (BLAs Only) ☒
DARRTS

Version: 12/9/2011

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/s/

AMY R TILLEY
01/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM** **Requesting same Reviewers as Palbociclib sNDA 207103/002** **Nicholas Senior & Jessica Cleck-Derenick**	FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Tilley/RPM, OHOP/DOP1/301-796-3994

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
1-29-16		sNDA 21344/26	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Faslodex (fulvestrant)	Yes		Since a "near simultaneous" review is being done with Palbociclib the request date is the same as sNDA 207103/002.

NAME OF FIRM:	
AstraZeneca Pharmaceuticals LP	PDUFA Date: **Target Date: 2-29-16**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☒ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION – Adding Indication

For OSE USE ONLY
☐ REMS

EDR link to submission: **\\CDSESUB1\evsprod\NDA021344\021344.enx**

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: Virtual Meeting 1-20-16
Labeling Meetings: February 2, 16, and 18, 2016 – combined with Palbociclib label meetings
Wrap-Up Meeting: N/A

SIGNATURE OF REQUESTER
Amy Tilley *{See appended electronic signature page}*

12/15/2014

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND

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/s/

AMY R TILLEY
01/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☒ Both ☐ DOP1 Requests Miriam Dinatale / Tamara Johnson			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Amy Tilley, OHOP/DOP1/301-796-3994	
DATE 1-29-16	IND NO.	NDA/BLA NO. sNDA 21344/026	TYPE OF DOCUMENT PI	DATE OF DOCUMENT 11-17-15
NAME OF DRUG Faslodex (fulvestrant)	NAME OF FIRM AstraZeneca Pharmaceuticals LP		CLASSIFICATION OF DRUG	PDUFA Goal Date Target Date 2-29-16 (near simultaneous review with Palbociclib sNDA 207103/002 and Faslodex PLLR S-025)
Requested Consult Completion Date: 2-29-16	☐ Urgent* (< 14 days)		☒ Priority (14-29 days)	☐ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): **\\CDSESUB1\evsprod\NDA021344\021344.enx**	Materials to be reviewed: PI

1. Please briefly describe the submission including drug's indication(s):
Efficacy Supplement-026 Faslodex is in combination with palbociclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative [redacted] (b) (4)

2. Describe in detail the reason for your consult. Include specific questions:
To assist in revising the Faslodex S-026 PI into PLLR format. This Efficacy Supplement-026 will have a "near simultaneous" review with Palbociclib sNDA 207103/002 and Faslodex PLLR sNDA 21344/S-025.

3. Meeting dates:
Labeling: February 2, 16, and 18, 2016

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years): Reference ID: 3843329

Review Team:
Project Manager: Amy Tilley
Clinical Reviewer & Team Leader: Eff Suparna Wedam / Safety Amanda Walker / Laleh Amiri-Kordestani
Pharmacology/Toxicology reviewer & Team Leader: Kimberly Ringgold / Todd Palmby
Clinical Pharmacology Reviewer & Team Leader: Jeanne Fourie-Zirkelbach / Wentao Fu / Qi Liu
MHT: Miriam Dinatale / Tamara Johnson

PRINTED NAME or SIGNATURE OF REQUESTOR:	METHOD OF DELIVERY (Please check)
Amy Tilley *{See appended electronic signature page}*	☒ DARRTS ☒ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 10/14/2014

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/s/

AMY R TILLEY
01/29/2016

From: Tilley, Amy
To: "Mercer, Elinore"
Cc: Wheeler, Charlene
Subject: RE: sNDA 21344/26 Faslodex-Labeling & PREA Waiver
Date: Thursday, January 28, 2016 5:07:42 PM

Elinore, it is our intent for supplement 26 to have a "near simultaneous" review with both Pfizer's sNDA 207103 submitted Oct 14, 2015, as well as the Faslodex PLLR supplement 25. All three labels are currently under review, therefore we are unable to provide the timing of our label negotiations at this time.

We just received word today from our PeRC Staff that we will allow Faslodex supplement 26 to reference Pfizer's Agreed iPSP for NDA 207103. However, your request for a full pediatric waiver for the breast cancer indication will still need to be reviewed by our PeRC staff. Our decision on the full pediatric waiver request will be forth coming in the action letter for this supplement.

Unfortunately, at this time our application database is experiencing technical problems, however I will notify you as soon as I can verify the full waiver request has been received.

Regards.
Amy

From: Mercer, Elinore [mailto:elinore.mercer@astrazeneca.com]
Sent: Thursday, January 28, 2016 2:21 PM
To: Tilley, Amy
Cc: Wheeler, Charlene
Subject: RE: sNDA 21344/26 Faslodex - Filing Letter

Dear Amy,
I am confirming receipt and would like to thank you for providing the Filing Letter ahead of schedule!

Per the Written Responses from the Agency in response to AstraZeneca's Type B meeting request (19 Aug 2015), we were anticipating "near-simultaneous" review and approval with Pfizer's sNDA (20-7103, submitted 14 Oct 2015) for PALOMA-3. Therefore, please provide guidance regarding the timing of the anticipated negotiation of our label.

We acknowledge that there are two FASLODEX labels currently under review with the Agency: 21344/25, submitted 28 Oct 2015 (PLLR update) and 21344/26, submitted 17 Nov 2015 (PALOMA-3 efficacy supplement). The PLLR supplement (21344/25) was a standalone submission which now we would like to bundle with the PALOMA-3 sNDA label (21344/26). As such, we will submit an updated single version of the label to FDA by the requested timeline of 09 Feb 2016 if not earlier.

Regarding the PREA requirement noted in the filing letter, we would like to confirm if you've received our full waiver request (21344/26, Sequence 0103, 26 Jan 2016) and if this is sufficient or if anything additional is needed.

Kind regards,
Elinore

Elinore M. Mercer, Ph.D., R.A.C.
Director, Regulatory Affairs, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
(858) 945-6127
elinore.mercer@astrazeneca.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, January 28, 2016 1:26 PM
To: Mercer, Elinore <elinore.mercer@astrazeneca.com>
Subject: sNDA 21344/26 Faslodex - Filing Letter
Importance: High

Elinore, attached is the Filing Letter regarding sNDA 21344/26 Faslodex.

Regards.
Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/29/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344/S-026

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

AstraZeneca Pharmaceuticals LP
Attention: Elinore Mercer, PhD
Director, Global Regulatory Affairs
1800 Concord Pike
Wilmington, DE 19803

Dear Dr. Mercer:

Please refer to your supplemental New Drug Application (sNDA) dated November 17, 2015, received November 17, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Faslodex Injection (fulvestrant) Solution for Injection 250 mg/5 mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 16, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 20, 2016. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. Regarding Adverse Reactions in Highlights, [redacted] (b) (4)
2. The package insert (PI) is not in PLLR format. You must submit the revised PI that complies with all labeling requirements specified in 21 CFR 201.56 and 201.57. Specific details on the affected sections of labeling, the implementation schedule, FAQs, and other resources, including the PLLR and draft guidance, can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 9, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indications proposed in this supplemental application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, M.D.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GEOFFREY S KIM
01/28/2016

From: Tilley, Amy
To: "elinore.mercer@astrazeneca.com"
Subject: RE: Time Sensitive re sNDA 21344-26 - Need PI in Word format
Date: Friday, January 22, 2016 2:32:05 PM

Also please state in your cover letter whether or not there will be any changes to your carton or container labels. If so, please officially submit the carton and container labels as well.

Regards.

Amy

From: Tilley, Amy
Sent: Friday, January 22, 2016 2:30 PM
To: 'elinore.mercer@astrazeneca.com'
Subject: Time Sensitive re sNDA 21344-26 - Need PI in Word format

Elinore,

Please officially submit the PI in Word format by 4 pm Tuesday, Jan 26, 2016, to the sNDA.

You should receive the filing notification by the end of next week.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/22/2016

From: Tilley, Amy
To: "elinore.mercer@astrazeneca.com"
Bcc: Kacuba, Alice
Subject: URGENT re sNDA 21344-26 Faslodex - PREA Waiver
Date: Friday, January 22, 2016 12:24:31 PM
Importance: High

Elinore,

Regarding this reverse parallel label Efficacy Supplement submitted on 11-17-15, we are unable to locate the PREA Waiver Request within this supplement. If one was submitted, please let us know it's location within the submission.

Furthermore, why was PREA not addressed via an Initial PSP (iPSP) submission?

Please respond to this email asap.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley|Regulatory Project Manager|Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2108|Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax)|✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
01/22/2016

From: O"Donnell, Jeannette
To: "Mercer, Elinore"
Cc: Tilley, Amy
Subject: RE: FDA Communication: sNDA 21344-026/Fulvestrant/IR - Time Sensitive
Date: Friday, January 15, 2016 3:32:00 PM
Importance: High

Dear Elinore,

Please see our answers below:

- On January 20, 2016, would you like us to provide a response document, new draft annotated and non-annotated labels, and final label, or simply the response document?
  FDA Response: At this time a response document is sufficient, we do not yet need you to provide a new label
- If you would like us to provide new labels, should we provide the updates using the draft labels submitted on November 17, 2015, in sNDA 21344 (Sequence No 0099) or the draft labels submitted in sNDA 21344-025 on October 28, 2015?
  FDA Response: Please see answer to bullet one
- Should our cover letter reference sNDA 21344-026 or sNDA 21344-025?
  FDA Response: Please go ahead and refer to both supplements in your cover letter
- Does the Agency have any further updates regarding sNDA submitted on November 17, 2015? We have not yet received formal acknowledgement or confirmation of filing.
- **FDA Response: Your application project manager Amy Tilley will respond to this when she returns next week.**

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

From: Mercer, Elinore [mailto:elinore.mercer@astrazeneca.com]
Sent: Friday, January 15, 2016 2:58 PM
To: O'Donnell, Jeannette
Cc: Tilley, Amy
Subject: RE: FDA Communication: sNDA 21344-026/Fulvestrant/IR - Time Sensitive

Dear Jeannette,
This email is in regards to the phone message I left on January 15, 2016, regarding your request re: NDA 21344-026. As our team works to prepare our January 20, 2016 response, I would like to confirm several things:

- On January 20, 2016, would you like us to provide a response document, new draft annotated and non-annotated labels, and final label, or simply the response document?
- If you would like us to provide new labels, should we provide the updates using the draft labels submitted on November 17, 2015, in sNDA 21344 (Sequence No 0099) or the draft labels submitted in sNDA 21344-025 on October 28, 2015?
- Should our cover letter reference sNDA 21344-026 or sNDA 21344-025?
- Does the Agency have any further updates regarding sNDA submitted on November 17, 2015? We have not yet received formal acknowledgement or confirmation of filing.

Thank you Jeannette, and have a wonderful holiday weekend!

Kind regards
Elinore

Elinore M. Mercer, Ph.D., R.A.C.
Director, Regulatory Affairs, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
(858) 945-6127
elinore.mercer@astrazeneca.com

From: Mercer, Elinore
Sent: Thursday, January 14, 2016 10:07 AM
To: 'O'Donnell, Jeannette' <Jeannette.Odonnell@fda.hhs.gov>
Cc: Tilley, Amy <Amy.Tilley@fda.hhs.gov>; Lowry, Helen <Helen.Lowry1@astrazeneca.com>
Subject: RE: FDA Communication: sNDA 21344-026/Fulvestrant/IR - Time Sensitive

Dear Jeannette,
I confirm receipt of the information request regarding NDA 021344/S-026 below. We will plan to communicate our response via email by COB January 20, 2016, and will also set-up a formal submission. Please do not hesitate to reach out with any further questions or comments.

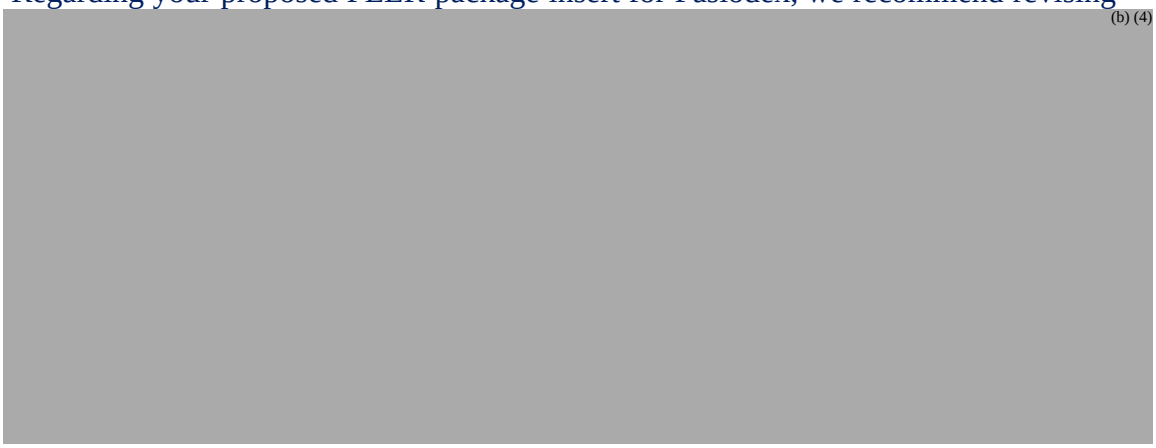
Kind regards,
Elinore

From: O'Donnell, Jeannette [mailto:Jeannette.Odonnell@fda.hhs.gov]
Sent: Thursday, January 14, 2016 9:49 AM
To: Mercer, Elinore <elinore.mercer@astrazeneca.com>
Cc: Tilley, Amy <Amy.Tilley@fda.hhs.gov>
Subject: FDA Communication: sNDA 21344-026/Fulvestrant/IR - Time Sensitive
Importance: High

Dear Elinore,

On behalf of Amy Tilley and in reference to NDA 021344/S-026 we have the following information request:

- Regarding your proposed PLLR package insert for Faslodex, we recommend revising (b) (4)



Please respond by **COB Wednesday, January 20, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA. As I am currently covering for Amy Tilley, Regulatory Project Manager for this application, please reply to all.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
01/15/2016

From:	O"Donnell, Jeannette
To:	"Mercer, Elinore"
Cc:	Tilley, Amy
Subject:	FDA Communication: sNDA 21344-026/Fulvestrant/IR - Time Sensitive
Date:	Thursday, January 14, 2016 9:49:00 AM
Importance:	High

Dear Elinore,

On behalf of Amy Tilley and in reference to NDA 021344/S-026 we have the following information request:

- Regarding your proposed PLLR package insert for Faslodex, we recommend revising

(b) (4)

[redacted]

Please respond by **COB Wednesday, January 20, 2015**. Please respond by 1) email to facilitate review 2) formal submission to the NDA. As I am currently covering for Amy Tilley, Regulatory Project Manager for this application, please reply to all.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

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/s/

JEANNETTE L O'DONNELL
01/14/2016

From: O"Donnell, Jeannette
To: "Mercer, Elinore"
Cc: Lowry, Helen; Tilley, Amy
Subject: RE: sNDA 21-344, sequence no. 0099
Date: Monday, December 21, 2015 10:10:00 AM
Importance: High

Dear Elinore,

Thank you for contacting us regarding your supplement for NDA 021244, submitted on November 17, 2015. We are in receipt of your application and it is under review. At this time we have no feedback, we will contact you as the review progresses if this changes.

Sincerely,

Jeannette O'Donnell
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)/Office of Hematology and Oncology Products
OND/CDER/FDA
Phone: 240-402-4978
Fax: 301-796-9845
Email: Jeannette.Odonnell@fda.hhs.gov

From: Mercer, Elinore [mailto:elinore.mercer@astrazeneca.com]
Sent: Monday, December 21, 2015 9:56 AM
To: O'Donnell, Jeannette
Cc: Lowry, Helen; Tilley, Amy
Subject: FW: sNDA 21-344, sequence no. 0099

Dear Jeannette,
I am reaching out to you in Amy Tilley's absence as per her Out of Office response below.

I am writing regarding the status of the AstraZeneca's sNDA 21-344 (Sequence No. 0099) submitted on Nov 17, 2015, seeking a reverse parallel labeling extension for fulvestrant on the basis of PALOMA-3 data submitted in Pfizer sNDA 20-7103 (dated October 14, 20150). We are wondering if there is any feedback from the Agency regarding our submission or plans moving forward for this unique review process.

Thank you, and have a great day!

Kind regards,
Elinore

Elinore Mercer, Ph.D., R.A.C.
Director, Regulatory Affairs, Oncology

AstraZeneca | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
(858) 945-6127
elinore.mercer@astrazeneca.com

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Monday, December 21, 2015 9:50 AM
To: Mercer, Elinore <elinore.mercer@astrazeneca.com>
Subject: Automatic reply: sNDA 21-344, sequence no. 0099

I am out of the office from 3:00 pm.12-18-15 and returning 1-4-16.

On 12-21-15 please contact either Jeannette O'Donnell at 240-402-4978 / jeannette.odonnell@fda hhs.gov or Frank Cross at 301-796-0876 / frank.crossjr@fda.hhs.gov.

From 12-22-15 - 12-31-15 please contact Frank Cross at 301-796-0876 or frank.crossjr@fda hhs.gov.

For emergencies please contact Alice Kacuba at 301-796-1381 or alice.kacuba@fda hhs.gov.

Thank you and Happy Holidays!

Amy Tilley

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/s/

JEANNETTE L O'DONNELL
12/21/2015