NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	209092/S-018 209935/S-027
Priority or Standard	Priority (priority review voucher used) for NDA 209092/S-018 Standard for NDA 209935/S-027
Submit Date(s)	209092/S-018: 12/22/2023 209935/ S-027: 3/11/2024
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PDUFA Goal Date	209092/S-018: 9/22/2024 209935/ S-027: 1/11/2025
Division/Office	DO1/OOD
Review Completion Date	*Electronic Stamp Date*
Established Name	209092: Ribociclib 209935: Ribociclib and letrozole
Trade Name	209092: Kisqali 209935: Kisqali Femara Co-Pack
Pharmacologic Class	Kinase Inhibitor (ribociclib) Aromatase Inhibitor (letrozole)
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	Ribociclib: 200 mg tablets Letrozole: 2.5 mg mg tablet
Dosing Regimen	Ribociclib: 400 mg (two 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles. Letrozole: 2.5 mg (one tablet) taken once daily throughout the 28-day cycle.
Proposed Indication(s)	(b) (4)
FDA Recommended Indication(s)	209092: KISQALI is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with

	hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence. 209935: KISQALI FEMARA CO-PACK is indicated for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.
Recommendation on Regulatory Action	Regular Approval

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
PLT=Patient Labeling Team
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
RPBM = Regulatory Business Process Manager

Glossary

aBC	advanced breast cancer
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
ANC	absolute neutrophil count
BC	breast cancer
BCRP	Breast cancer resistance protein (transporter)
BSEP	Bile salt export pump (transporter)
CDK4/6	Cyclin-dependent kinase 4/6
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCO	data cut-off
DDFS	distant disease-free survival
DFS	disease-free survival
DRFS	distant recurrence-free survival
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRS	electronic case retrieval strategy
eCTD	electronic common technical document
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ET	endocrine therapy
ET only arm/group	letrozole or anastrozole, plus goserelin (if applicable)
FDA	Food and Drug Administration
GCP	good clinical practice
HER2	Human epidermal growth factor receptor 2
HR	hormone receptor
iDFS	invasive disease-free survival
ILD	interstitial lung disease
IRT	interactive response technology
IND	Investigational New Drug
MATE1	Multidrug and toxin extrusion protein 1 (transporter)
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NSAI	nonsteroidal aromatase inhibitor
OCT2	Organic cation transporter 2
OS	overall survival
PARP	Poly (ADP-ribose) polymerase
PBPK	physiologically-based pharmacokinetic (model)
PD	pharmacodynamics
PFS	progression-free survival

PgR	progesterone receptor
PI	prescribing information
popPK	population pharmacokinetics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPS	per protocol set
PRO	patient reported outcome
PSUR	periodic safety update report
RFS	recurrence-free survival
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
SC	Steering Committee
SCE	summary of clinical efficacy
SCP	summary of clinical pharmacology
SCS	summary of clinical safety
SEER	Surveillance, Epidemiology, and End Results
SOC	system organ class
SPM	second primary malignancies
STEEP	Standardized Definitions for Efficacy End Points (in Adjuvant Breast Cancer Trials)
TTR	time to response
TEAE	treatment emergent adverse event
VPC	visual predictive checks

1. Executive Summary

1.1 Product Introduction

The FDA review team recommends regular approval for ribociclib in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.

Ribociclib (Kisqali) is an oral inhibitor of cyclin-dependent kinase (CDK) 4 and 6. It was first approved for marketing authorization in the United States in 2017 for advanced or metastatic HR+, HER2-negative breast cancer, and subsequently approved in many countries globally. The current approved indications for ribociclib are:

KISQALI is indicated for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- *an aromatase inhibitor as initial endocrine-based therapy; or*
- *fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.*

The Applicant proposed the following new indication in a supplemental new drug application (sNDA) for 209092 (ribociclib) and 209935 (ribociclib and letrozole co-pack):

(b) (4)

1.2 Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence. The Applicant conducted a single randomized (1:1) multicenter trial (NATALEE) in the adjuvant treatment of patients with HR+, HER2-negative stage II and III early breast cancer at high risk of recurrence. The trial included patients with any lymph node involvement (excluding microscopic nodal involvement), or if there was no nodal involvement, either tumor size > 5 cm, or tumor size 2 to 5 cm with either Grade 2 (and high genomic risk or Ki67 ≥ 20%) or Grade 3. Randomization was stratified by menopausal status (men and premenopausal women vs postmenopausal women), AJCC 8th edition anatomic stage group (II vs III), prior (neo)adjuvant chemotherapy (yes vs. no), and geographical region (North America, Western Europe, Oceania vs rest of the world). Patients were randomized to receive ribociclib + endocrine therapy (ET, non-steroidal aromatase inhibitor [NSAI] and goserelin in men and premenopausal women) vs. ET only. Ribociclib was administered at 400 mg daily 3 weeks on/1 week off for up to 36 months (3 years) or until

disease recurrence or unacceptable toxicity occurred. Endocrine therapy was given per standard of care for a total duration of at least 60 months (5 years).

The primary endpoint of NATALEE was invasive disease-free survival (iDFS) by investigator in the intent to treat (ITT) population. Final iDFS analysis was planned at 500 events with 93% power to detect a hazard ratio of 0.73 at a one-sided alpha of 0.025 using a stratified log-rank test. Three interim analyses (IA) for iDFS were planned:

- IA1: for futility at 40% iDFS events
- IA2: for efficacy superiority at 70% iDFS events
- IA3: for efficacy superiority at 85% iDFS events

Secondary endpoints included overall survival (OS), although the trial was not powered for OS, and OS was not formally tested. OS analysis was planned at iDFS IA2 and IA3 if the efficacy boundary were crossed, and at the final analysis of iDFS. A total of 2549 patients were randomized to the ribociclib + ET arm and 2552 patients were randomized to the ET only arm.

The trial met its primary endpoint of iDFS at IA3 demonstrating a statistically significant improvement in iDFS (hazard ratio [HR] 0.748, 95% confidence interval [CI] 0.619-0.906). The 3-year iDFS was 90.4% (88.6-91.9) on the ribociclib + ET arm compared to 87.1% (85.3-88.8) on the ET only arm, for an absolute difference of 3.3%. However, at IA3, there was a large amount of censoring for iDFS, as only 20% of patients had completed 3 years of adjuvant ribociclib. Thus, there was a concern for possible diminishing iDFS effect with longer follow-up. Additionally, OS was immature with 134 total events (OS HR 0.759, 95% CI 0.539-1.068), and there were more treatment-emergent adverse events (TEAEs) and deaths on the ribociclib + ET arm compared to the ET only arm. Due to these concerns, FDA requested the Applicant continue NATALEE until the final iDFS analysis, and to conduct an additional OS analysis at the time of final iDFS analysis.

The sNDA submission for 209092/S-018 was received on December 22, 2023. The Applicant used a priority review voucher (PRV). The sNDA submission for 209935/S-027 was received on March 11, 2024, and cross-references sNDA 209092/S-018. The sNDA submissions are based on final iDFS of the NATALEE trial, with a data-cutoff date of July 21, 2023. At the final iDFS analysis, the iDFS HR was 0.749 (95% CI 0.628-0.892). While the median iDFS was not estimable on either treatment arm, the 3-year iDFS rates were 90.7% (95% CI: 89.3, 91.8) in the ribociclib + ET arm and 87.6% (95% CI: 86.1, 88.9) in the ET only arm. The interim OS analysis at the time of final iDFS remained immature with 84 deaths (3%) on the ribociclib + ET arm and 88 deaths (3%) on the ET only arm; the OS HR was 0.89 (95% CI 0.66-1.20) with median OS not estimable.

The overall safety data was consistent with the known adverse event (AE) profile of ribociclib + ET, but the incidence and severity of most AEs was lower, likely due to the lower dose of ribociclib used in the adjuvant setting, as well as a generally healthier adjuvant population. As of July 21, 2023 data-cut off, 43% patients had completed ≥3 years of ribociclib + ET and 69% had completed ≥2 years of ribociclib + ET. Deaths on treatment were uncommon overall but higher on the ribociclib + ET arm, with 20 deaths (0.8%) compared to 9 deaths (0.4%) on the ET only arm. Adverse events of special interest (AESI) were analyzed, including hepatobiliary toxicity,

interstitial lung disease/pneumonitis, QT prolongation, and severe cutaneous adverse reactions, and were consistent with the known toxicity profile of ribociclib + ET. Secondary malignancies were also analyzed given the ongoing nitrosamine impurity level issues at the time of the sNDA submission, with no meaningful differences detected in NATALEE, although secondary malignancy due to nitrosamine exposure is not expected for years if not decades following exposure. The safety update submitted on March 21, 2024 had a data-cut off of October 26, 2023, and safety findings were consistent with those at final iDFS.

The (b) (4) impurity ((b) (4)) is a nitrosamine drug substance related impurity (NDSRI) found in ribociclib succinate drug substance and in the drug product. The impurity level found in ribociclib tablets is higher than those recommended by ICH S9 for patients with early-stage cancer. Using the predicted Carcinogenic Potency Categorization Approach, (b) (4) is considered carcinogenic potency category 3 with a recommended acceptable intake limit of (b) (4) ng/day per the FDA's final guidance: *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (August 2023)*.

On March 6, 2024, FDA placed all early breast cancer trials of ribociclib under IND 117796 on partial clinical hold, including the NATALEE trial. Hold deficiencies and information to resolve the deficiencies included insufficient information to assess risks to human subjects based on the available mutagenicity data at that time, and the investigator brochure lacking information on the potential risks and harms of the nitrosamine impurity levels. The Applicant was informed that they must issue a Dear Investigator Letter, reconsent all patients receiving ribociclib for treatment of their early breast cancer, and update the Investigator's Brochure to address the partial clinical hold.

To justify the nitrosamine impurity level, the Applicant conducted in vitro and in vivo tests to establish an acceptable intake level. An Enhanced Ames Test (EAT) did not show (b) (4) to be mutagenic. The Applicant also conducted an *in vivo* transgenic gene mutation assay in the Muta™Mice to evaluate the genotoxic potential of (b) (4) in bone marrow, liver, kidney, and the duodenum. The organs were selected to be in compliance with the OECD 488 guideline. Male and female mice were administered (b) (4) at doses of 100 mg/kg/day to females and 25, 50, or 100/80 mg/kg/day to males. On April 8, 2024, the Applicant notified the FDA of initial results of the *in vivo* Muta™Mice mutagenicity study. The study found that following administration of the nitrosamine impurity (b) (4) to male mice, statistically significant increases in mutant frequency were observed across all dose levels in the duodenum when compared to control animals. On April 26, 2024, the Applicant notified the FDA updated results of the *in vivo* Muta™Mice mutagenicity study, which found that following administration of the nitrosamine impurity (b) (4) to male and female mice, statistically significant increases in mutant frequency were observed across all dose levels in the liver and duodenum when compared to control animals. The Applicant requested a Type A CMC meeting (held May 13, 2024) to discuss their proposed manufacturing changes to address the (b) (4) impurity levels to limit the maximum acceptable intake limit of (b) (4) to (b) (4) ng/day, corresponding to a maximum of (b) (4) ppm intake. The proposed manufacturing changes include (b) (4) refrigerating (b) (4) drug product, (b) (4) and limiting the shelf-life of drug product.

Between May and September 2024, the Applicant updated the manufacturing process for ribociclib to decrease the (b) (4) impurity level to the acceptable intake limit. The manufacturing updates include:

- (b) (4)
- refrigerating drug product prior to dispensing to patients (drug product can be stored at room temperature for up to 2 months after dispensing to patients);
- decreasing storage shelf life to 12 months.

During the review of the sNDA, the Applicant provided additional stability data to support the proposed control strategy for (b) (4). With these updated manufacturing processes, the Applicant is proposing an acceptable intake limit of no more than (b) (4) ng/day for all patients with breast cancer, including for patients with advanced or metastatic breast cancer. The Applicant's marketing plan for newly manufactured ribociclib tablets with lower levels of (b) (4) include:

(b) (4)

The Applicant confirmed on September 9, 2024 via an information request sent by FDA that all commercially available ribociclib that contained the higher levels of (b) (4) was depleted at all commercial pharmacies, and only ribociclib with lower levels of (b) (4) at or below the acceptable intake limit are commercially available.

With the updated manufacturing processes, the (b) (4) impurity level is now within the acceptable intake limit. The review teams recommend Regular Approval for ribociclib, with the following indication:

209092: *KISQALI is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.*

209935: *KISQALI FEMARA CO-PACK is indicated for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.*

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer and second leading cause of cancer deaths in women in the United States. Early-stage HR+, HER2-negative breast cancer is treated with curative intent, but can recur and is incurable if it recurs with distant metastases, which occurs in about 30% of patients. The standard of care treatment for patients with early HR+, HER2-negative breast cancer includes surgery +/- radiation therapy and (neo)adjuvant chemotherapy, followed by at least 5 years of adjuvant endocrine therapy +/- abemaciclib. Ribociclib for the adjuvant treatment of patients with early breast cancer provides an additional treatment option for a serious and life-threatening disease, and generally does not cause diarrhea, which is seen with abemaciclib. The NATALEE trial enrolled patients with stage II and III early breast cancer that was HR+, HER2-negative. Patients received ribociclib plus endocrine therapy or endocrine therapy only. Ribociclib was administered for up to 3 years at 400 mg daily for 21 days on/7 days off. The NATALEE trial demonstrated a statistically significant improvement in iDFS for patients with early-stage HR+, HER2-negative breast cancer at IA3 with a hazard ratio of 0.748 (95% CI 0.619-0.906). At the final iDFS analysis, the iDFS HR was 0.749 (95% CI 0.628-0.892). OS was not formally tested, and the study was not powered for OS. OS results remain immature at the time of the final iDFS analysis; the OS trend favors the ribociclib plus endocrine therapy arm (hazard ratio 0.89, 95% CI 0.66-1.20). No new safety signals were identified and those observed in the NATALEE trial are known adverse reactions associated with use of ribociclib + ET. With the updated manufacturing processes, the (b) (4) impurity level is now within the acceptable intake limit. Overall, the benefit/risk is favorable, and the FDA review teams recommend granting Regular Approval, for the following proposed indication:

209092: *KISQALI is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.*

209935: *Kisqali Femara Co-Pack is indicated for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Breast cancer is the most common cancer and second leading cause of cancer death in women in the U.S., with over 297,790 new cases and 43,170 deaths in 2023. • ~ 70% of patients with breast cancer have HR+, HER2-neg disease. • Early-stage HR+, HER2-neg breast cancer is treated with curative intent, but it is incurable if it recurs with distant metastases.	Early-stage HR+, HER2-neg breast cancer is a serious and life-threatening condition.

Current Treatment Options	• Standard of care treatment of early-stage HR+, HER2-neg breast cancer includes surgery ± radiation therapy and (neo)adjuvant chemotherapy followed by 5+ years of adjuvant endocrine therapy with or without abemaciclib. • Patients will receive an aromatase inhibitor or tamoxifen, with or without GnRH agonist depending on the primary treatment, sex, and menopausal status. • Adjuvant cytotoxic chemotherapies including taxanes, anthracycline-based regimens, or sequential use of these chemotherapies are also used. • Abemaciclib is approved in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence. • Despite these therapeutic options, approximately 30% of patients will relapse and develop metastatic disease.	Abemaciclib is approved for patients with node-positive early breast cancer, but can have significant side effects including diarrhea. Additional therapies for patients with early stage HR+, HER2-negative breast cancer are needed to improve long-term outcomes.
Benefit	• The NATALEE trial enrolled patients with stage II and III early breast cancer that was HR+, HER2-negative. Patients received ribociclib plus endocrine therapy or endocrine therapy only. Ribociclib was administered for 3 years at 400 mg daily for 21 days on/7 days off. • The NATALEE trial demonstrated a statistically significant improvement in iDFS for patients with early-stage HR+, HER2-negative breast cancer at IA3 with a hazard ratio of 0.748 (95% CI 0.619-0.906). At the final iDFS analysis, the iDFS HR was 0.749 (95% CI 0.628-0.892). • OS was not formally tested, and the study was not powered for OS. OS results remain immature at the time of final iDFS analysis. • The OS trend favors the ribociclib plus endocrine therapy arm (HR 0.89, 95% CI 0.66-1.20).	Adjuvant treatment of high-risk early breast cancer (stage II and III) with ribociclib added to endocrine therapy produced a statistically significant improvement in iDFS compared to ET alone. OS remains immature.

Risk and Risk Management	• No new safety signals were observed compared to the known safety profile of ribociclib and endocrine therapy in the metastatic setting. • There was no apparent increase in incidence of secondary malignancies. • With the updated manufacturing processes, the (b) (4) impurity levels are now within the acceptable intake limit.	The safety profile of adjuvant ribociclib + ET is acceptable for the indicated patient population, and safe use can be managed through labeling. There is no indication for REMS.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

x	The patient experience data that was submitted as part of the application, include:				**Section Location**
	x	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	Section 8.1.2
			□	Observer reported outcome (ObsRO)	N/A
			□	Clinician reported outcome (ClinRO)	N/A
			□	Performance outcome (PerfO)	N/A
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group			N/A
	□	Patient-focused drug development or other stakeholder meeting summary			N/A
	□	Observational survey studies designed to capture patient experience data			N/A
	□	Natural history studies			N/A
	□	Patient preference studies (e.g., submitted studies or scientific publications)			N/A
	□	Other: (Please specify)			N/A
□	Patient experience data that was not submitted in the application, but was considered in the review considered in this review.				

X _____

Jennifer Gao, MD

Cross-Disciplinary Team Lead

2. Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Breast cancer (BC) is the most frequently diagnosed cancer worldwide. Approximately 2.3 million new cases of BC and 685,000 deaths attributed to this disease were estimated to occur in 2020 worldwide. Breast cancer incidence varies between individuals of different ethnicities and in different geographic locations around the world, with age-standardized world incidence rates per 100,000 ranging from 26.2 for South-Central Asia to 95.5 for Australia and New Zealand (GLOBOCAN 2020). In the United States, BC is projected to be the most common cancer diagnosed in 2023 with an estimated incidence of 297,790 new cases and 43,170 deaths (SEER 2023). Across Europe, the estimated incidence of BC in 2020 was approximately 531,000, with 142,000 deaths (GLOBOCAN 2020). Breast cancer in men is uncommon, with a reported frequency of approximately 1% of all BC (Eggemann et al 2013).

Almost all newly diagnosed BC cases are early BC (eBC), localized to the breast tissue and regional lymphatics, which are potentially curable with surgical resection and a variety of treatment modalities. Based on SEER Program data collected between the years 2010 and 2019, among all HR-positive, HER2-negative breast cancer cases in females, 94.8% of cases diagnosed were eBC, with 68.9% localized to the breast tissue and 25.9% within both the breast tissue and regional lymph nodes (SEER 2022).

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of breast cancer worldwide and in the U.S. HR+, HER2-negative breast cancer is the most common subtype, and early-stage disease is treated with curative intent.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Besides primary surgery, systemic management of patients with HR-positive, HER2-negative eBC consists of additional antineoplastic treatment modalities including adjuvant endocrine therapy/aromatase inhibitor (ET/AI: letrozole, anastrozole or exemestane) or tamoxifen, radiotherapy, and neoadjuvant and/or adjuvant chemotherapy, typically considered for patients at risk for recurrence. The need for and selection of systemic adjuvant therapies is based on each individual's risk of recurrence and is guided by several clinical, pathological and genomic predictive and prognostic considerations. Specifically, patients considered to be at increased risk for recurrence include anatomic stage Group II and III disease with larger tumor size and/or metastases in multiple regional lymph nodes, high tumor grade, and high recurrence genomic score, or a combination of these. Adjuvant systemic treatments, including multiagent chemotherapy and hormonal therapy in patients with eBC decrease locoregional and distant recurrences, and have been shown to improve 15-year breast cancer mortality (Clarke et al 2005).

Adjuvant ET/AI or tamoxifen, independent of chemotherapy, has been shown to reduce the risk of recurrence and BC deaths (Clarke et al 2005), and has therefore been incorporated into clinical

guidelines as a recommended treatment for pre- and postmenopausal women with HR-positive eBC (Senkus et al 2015, NCCN 2019). Based on limited data, adjuvant AI or tamoxifen is also considered to be the treatment of choice for men with HR-positive, HER2-negative eBC (Zagouri et al 2015).

While the incorporation of adjuvant ET for the treatment of patients with HR-positive eBC has been shown to reduce the risk of recurrence and BC deaths (Clarke et al 2005), recurrences are still common, affecting approximately 30-60% of patients with Stage II and III disease (Bria et al 2010, Wangchinda, Ithimakin 2016, Gomis, Gawrzak 2017 Pan et al 2017). In a meta-analysis including more than 60,000 women with ER-positive eBC who were disease-free after 5 years of adjuvant ET, the cumulative 20-year risk of distant recurrence was 31% in those with 1-3 positive nodes (N1-3), and 52% in those with 4-9 positive nodes (N4-9). Additionally, the cumulative 20-year risk of distant recurrence in patients without nodal disease (N0) was 22%, indicating that these patients are also at risk for recurrence. The corresponding cumulative 20-year risks of death from BC based on nodal status (N0, N1-3, N4-9) were 15%, 28%, and 49%, respectively (Pan et al 2017).

Although the risk of recurrence in patients with HR-positive, HER-2 negative eBC is highest during the first 5 years after diagnosis, among those who recur, more than half experience late recurrences (≥ 5 years from diagnosis) (Bria et al 2010, Wangchinda, Ithimakin 2016, Gomis, Gawrzak 2017, Pan et al 2017). Disease recurrence typically presents as distant metastasis, which is generally incurable and will eventually lead to death due to BC (Pan et al 2017). Thus, prevention of both early and late recurrences are equally important considerations when making adjuvant treatment recommendations for patients with HR-positive, HER2-negative eBC.

Of note, Verzenio (abemaciclib), a CDK4/6 inhibitor in combination with ET (tamoxifen or an AI) is approved for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, eBC at high risk of recurrence.

These data, including the long-term persistent risk of disease recurrence despite adjuvant ET, highlight the need for new therapeutic strategies that are well tolerated and improve clinical outcomes in patients with HR-positive, HER2-negative Stage II and III eBC.

Table 1: Summary of treatment armamentarium relevant to proposed indication other than chemotherapy

Products Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments **Non-steroidal aromatase inhibitors**						

Letrozole (Femara)	Letrozole is indicated for: - Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. - Extended adjuvant treatment of postmenopausal women with early breast cancer, who have received prior standard adjuvant tamoxifen therapy.	2004	Recommended dose: 2.5.mg once daily Femara tablets are taken orally without regard to meals	vs. tamoxifen DFS: HR 0.79; 95% CI (0.68, 0.92); systemic DFS: HR 0.83; 95% CI (0.70, 0.97); time to distant metastasis: HR 0.73; 95% CI (0.60, 0.88); OS: HR 0.86; 95% CI (0.70, 1.06)	The most common adverse drug reactions (≥ 20%) were hot flashes, arthralgia, flushing, asthenia, edema, headache, dizziness, hypercholesterolemia, sweating increased, bone pain; and musculoskeletal	Initial accelerated approvals for adjuvant (2005) and extended adjuvant (2004) treatment received that was converted to full approval in 2010.
Anastrozole (Arimidex)	Anastrozole is indicated as monotherapy for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer	2002	One 1 mg tablet taken once daily	vs. tamoxifen or in combination with tamoxifen DFS: HR: 0.87, 95% CI (0.78, 0.97), HR-positive subgroup: HR 0.83, 95% CI: (0.73, 0.94). Of note, the combination of anastrozole and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen and is therefore not recommended to be administered	The most common adverse reactions (≥10%) were hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, peripheral edema and lymphedema, regardless of causality.	Priority review

				in combination.		
Steroidal aromatase inhibitors						
Exemestane (Aromasin®)	Exemestane is indicated as monotherapy for the adjuvant treatment of postmenopausal women with ER-positive early breast cancer who have received 2 to 3 years of tamoxifen and are switched to Aromasin for completion of a total of 5 consecutive years for adjuvant hormonal therapy.	2005	Recommended Dose: One 25 mg tablet once daily after a meal	vs tamoxifen DFS: HR: 0.69, 95% CI: (0.58, 0.82); HR-positive subpopulation DFS: HR: 0.65, 95% CI: (0.53, 0.79)	Most common adverse reactions (≥ 10%) were hot flushes, fatigue, arthralgia, headache, insomnia, and increased sweating.	
Selective estrogen receptor modulator						
Tamoxifen (Soltamox)	Tamoxifen is indicated as monotherapy for the adjuvant treatment of adult patients with early-stage ER-positive breast cancer.	2005	Recommended daily dose is 20 mg daily for 5-10 years.	The 10-year outcome data were reported in 1998 for 36,689 women in 55 randomized trials of another formulation of adjuvant tamoxifen using doses of 20 to 40 mg per day for 1 to 5+ years.	Most common adverse reactions: hot flashes, mood disturbance, vaginal discharge, vaginal bleeding, nausea, and fluid retention.	
CDK 4/6 inhibitor						

Abemaciclib (Verzenio)	Abemaciclib is indicated in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence.	2023	Recommended starting dose in combination with fulvestrant or an aromatase inhibitor: 150 mg twice daily. Verzenio tablets are taken orally with or without food.	vs ET alone Cohort 1 population: iDFS: HR: 0.653; 95% CI: (0.567, 0.753); 2-year IDFS rates of 85.5% (abemaciclib arm) versus 78.6% (control arm).	Most common adverse reactions (≥20%) were diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.	Priority Review
PARP inhibitor						
Olaparib (Lynparza)	Olaparib in indicated as monotherapy for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm HER2-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.	2022	Recommended dose: 300 mg taken orally twice daily, with or without food for up to 1 year.	vs placebo iDFS: HR 0.58; 95% CI: (0.46, 0.74); OS: HR 0.68; 95% CI: (0.50, 0.91). IDFS at 3 years was 86%; 95% CI: (82.8, 88.4) for patients receiving olaparib and 77%; 95% CI: (73.7, 80.1) for those receiving placebo.	Most common adverse reactions (≥10%) were nausea, fatigue (including asthenia), anemia, vomiting, diarrhea, decreased appetite, headache, dysgeusia, cough, neutropenia, dyspnea, dizziness, dyspepsia, leukopenia, and thrombocytopenia	Priority Review

Systemic treatment options other than chemotherapy are included.
Source: Femara USPI 2020, Arimidex USPI 2018, Aromasin USPI 2021, Soltamox USPI 2019, Verzenio USPI 2023, Lynparza USPI 2023

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the current treatment options for patients with early-stage HR+, HER2-negative breast cancer in the U.S. FDA concurs with the Applicant's assessment that additional treatment options are needed for this patient population, where treatment is given with curative intent.

As noted by the Applicant, more than half of recurrences of HR+, HER2-negative breast cancer occur ≥5 years after diagnosis. Due to the limited follow-up of the NATALEE trial, there is no information available at this time on whether addition of ribociclib to ET impacts the risk of these late recurrences.

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Kisqali® (ribociclib) was initially approved on 13-Mar-2017 in the US for the treatment of HR-positive/HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, based on results from Study A2301. Ribociclib was approved on 10-Dec-2021 in the US for use in men in combination with aromatase inhibitor as initial endocrine based therapy or fulvestrant as initial endocrine based therapy or following disease progression on ET in HR-positive, HER2-negative advanced or metastatic breast cancer.

Kisqali was also approved for an expanded indication on 18-Jul-2018 in the US based on results from Studies E2301 and F2301.

In the US, Kisqali is indicated for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men

Kisqali is also available in the US as part of the Kisqali® Femara® Co-Pack (ribociclib tablets co-packaged with letrozole tablets), approved on 04-May-2017.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the U.S. marketing history of ribociclib.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of the key interactions with the FDA are provided below:

- September 10, 2018: The protocol for Study CLEE011O12301C (Study O12301C) was submitted to FDA for the adjuvant treatment of early breast cancer on September 10, 2018 (SN 0806).
- October 18, 2018: The purpose of this Type B (EOPII) meeting was to seek FDA's advice on key aspects of the study design of Study O12301. Preliminary comments were received on November 08, 2018 and the meeting was ultimately cancelled by Novartis on November 16, 2018 as FDA agreed with Novartis questions and gave clear advice on the design of the trial.
- March 31, 2023: At the request of FDA, Novartis submitted topline data from the iDFS primary analysis (IA3).

- April 13, 2023: Novartis submitted a Preliminary Breakthrough therapy designation Request 2-pager which resulted in a 15 min meeting on April 26, 2023, to which the FDA recommended to not submit an official BTD application.
- April 21, 2023: Novartis submitted an RTOR request which was ultimately denied on April 26, 2023.
- May 15, 2023: Type B Briefing Book was submitted to discuss key clinical, safety, and operational components of the iDFS primary analysis (IA3) data to support a submission. FDA provided preliminary feedback on June 01, 2023, including that a substantial majority of patients had not yet completed 3 years of ribociclib and recommending Novartis wait to file until the final iDFS analysis in the coming months. On June 06, 2023, Novartis responded to FDA comments outlining key information on 'substantial majority of patients' and Overall Survival (OS) clarifications.
- June 14, 2023: Type B pre-submission meeting was held where Novartis's accepted the FDA recommendation to submit NATALEE based on the protocol-defied final iDFS analysis. It was agreed that at time of the final iDFS analysis, a substantial majority of patients would have completed the 3 years of ribociclib treatment. OS projections were also provided and it was noted that FDA may ask for additional information during the review, including but not limited to a PMC.
- September 19, 2023: Novartis submitted final iDFS analysis topline data to FDA. FDA requested Novartis to have an additional Type B pre-submission meeting to discuss the data.
- September 22, 2023: Novartis provided 90 days' notice of the intent to use a priority review voucher (PRV).
- September 28, 2023: Novartis submitted the Briefing Book for a second Type B pre-submission meeting, to be held on November 15, 2023. Preliminary comments were received on November 2, 2023 where FDA acknowledged the planned submission incorporating the final iDFS analysis results, and where alignment was reached on the high-level content of the submission. The Agency also agreed with the proposed 90-day safety update submission in March 2024. Additionally, FDA requested Novartis to (b) (4) .
- October 9, 2023: A CMC Type D meeting request was submitted to FDA to discuss nitrosamines in relation to Kisqali and the early breast cancer program. The Nitrosamine CMC meeting was held on November 15, 2023.
- November 15, 2023: During the type D meeting on 15-Nov-2023, FDA did not agree to an (b) (4) proposed by Novartis and indicated that negative Enhanced Ames Test (EAT) and MutaMouse (MM) study will be required for approval. FDA agreed to receive EAT and MM data during review.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the pre-submission regulatory activities above. However, in addition:

- **November 15, 2023: At the Type D CMC meeting, the FDA stated that the results of the EAT and Muta™Mice studies were needed as an important component of the sNDA review. FDA advised the Applicant that a major amendment may be necessary given the Applicant's use of a Priority Review Voucher and the fact that the draft and final Muta™Mice study reports were not expected until May and June 2024, respectively.**
- **January 22, 2024: At the Application Orientation Meeting, the FDA again emphasized the results of the Muta™Mice studies are needed as an important part of the sNDA review and that a major amendment may be necessary.**
- **February 14, 2024: Audited Draft Enhanced Ames Test (EAT) Report Submitted by the Applicant.**
- **March 6, 2024: EAT Final Report submitted by Applicant.**
- **March 6, 2024: During a teleconference with the Applicant, the FDA placed all early breast cancer trials, including NATALEE, on partial clinical hold, given the available data does not support the current nitrosamine impurity levels of ribociclib for patients with early-stage breast cancer. As part of the partial hold, no new patients may enroll, patients currently receiving ribociclib on these studies must be reconsented and made aware of the nitrosamine impurity level issues, a Dear Investigator Letter must be issued to all investigators regarding the nitrosamine impurity level issues, and the Investigator Brochure must be updated to include the nitrosamine impurity level issues. International regulatory agencies were made aware of the partial clinical hold. To address the partial hold issues, the Applicant must at a minimum submit the draft report of the Muta™Mice (MM) study for the FDA's review, followed by submission of the final MM study report as soon as possible.**
- **April 8, 2024: The Applicant notified the FDA by email of initial results of the *in vivo* Muta™Mice mutagenicity study. The study found that following administration of the nitrosamine impurity (b) (4) to male mice, statistically significant increases in mutant frequency were observed across all dose levels in the duodenum when compared to control animals.**
- **April 26, 2024: The Applicant notified FDA by email of updated results of the *in vivo* Muta™Mice mutagenicity study, which found that following administration of the nitrosamine impurity (b) (4) to male and female mice, statistically significant increases in mutant frequency were observed across all dose levels in the liver and duodenum when compared to control animals. The Applicant will issue a Dear Investigator Letter and reconsent all patients with early breast cancer who have received ribociclib.**
- **May 13, 2024: A Type A CMC meeting was held to discuss the next steps underway based on the recent MM results and nitrosamine impurity. The FDA discussed the**

Applicant's proposed manufacturing strategies to control the level of [redacted], including [redacted] changing drug product shelf-life storage duration to [redacted] months refrigerated and then 2 months at room temperature after it is dispensed to patients, and ongoing testing to ensure [redacted] levels are at or below [redacted] ng/day corresponding to maximum level of [redacted] ppm in the drug product. The Applicant indicated they will submit ~6 mo drug product stability data by September 2024 and will be submitting drug substance stability data as it is available.

- **May 17, 2024: The Applicant updated their website with the Direct Health Care Professionals Communication (DHPC) letter about important information regarding nitrosamine impurity levels related to investigational use of ribociclib in early breast cancer. The Applicant also indicated they would also send the letter to all providers.**
- **May 30, 2024: The Applicant submitted the report from the Muta™Mice study as well as CMC proposal to control [redacted] in the drug substance by adding a new test 'Specific impurity by HPLC-MS, [redacted]' with a limit of 'not more than [redacted] ppm' to the drug substance specifications. Due to different brand of mass spectrometry instruments, two alternative HPLCMS methods were developed, both of which are fully validated for the intended purpose per ICH Q2. The control of [redacted] in the drug product remains as previously proposed 'Specific impurity by HPLC-MS, [redacted]' with a limit of 'not more than [redacted] ppm.' Per the Applicant, drug substance stability data will be available in mid-July.**
- **June 6, 2024: An efficacy supplement major amendment letter was issued by the FDA, which extends the PDUFA goal date to September 22, 2024.**
- **June 25, 2024: The Muta™Mice final report was submitted to IND 117796 by the Applicant, with cross reference to NDA 209092 on June 26, 2024.**
- **May 30, 2024, June 13, 2024, July 3, 2024, July 15, 2024, August 12, 2024, August 27, 2024, August 29, 2024, September 3, 2024, and September 6, 2024: The Applicant submitted updated Drug Product and Drug Substance data and stability data for the FDA to review.**

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

4.1 Office of Scientific Investigations (OSI)

The FDA's Assessment:

A total of five NATALEE clinical trial sites, three in the U.S. (Site #s: 5007, 5057, and 5075) and two in Poland (Site #s: 1810 and 1811) were inspected by FDA. These sites included a total of 305 randomized patients.

At Site 1810, OSI noted several protocol deviations that were considered non-protocol deviations and not reported to the FDA. Per the site, protocol deviations were classified as "protocol" versus "non-protocol" deviations by the Applicant. The list of non-protocol deviations for this clinical investigator site was provided to Division of Oncology 1 (DO1), which concluded that the list included some deviations that would be considered protocol deviations. An information request was sent to the Applicant to provide the criteria that were given to Novartis or CRO employees for determining which reported protocol deviations should be reclassified as non-protocol deviations and not reported to FDA; to provide a summary of protocol deviations reported by the clinical investigator sites and then downgraded to non-protocol deviations by Novartis; and to clarify whether there were issues regarding protocol deviation reporting that were unique to Site 1810. The Applicant replied and stated that during the course of the NATALEE trial, there were updates to refine or add new types of protocol deviations, and also downgrade to a non-protocol deviation if it was felt the reported issue did not qualify as a protocol deviation. Upon review, the Applicant noted there were two protocol deviation codes amended during the conduct of NATALEE that may have led to downgrading of pre-existing protocol deviation issues:

Novartis PD ID	PD Criterion	Guidance on interpretation	Criteria or guidance on interpretation removed?	Could change lead to downgrading of PDs?	Rationale
EXCL08	Patient has not had resolution of all acute toxic effects of prior anti cancer therapies to CTCAE 4.03 ≤ Grade 1 at day of randomization. ~~except alopecia and amenorrhea and/or grade 2 neuropathy.~~	Acute refers to all non-chronic medical conditions per site's judgment. **Exceptions to this criterion: patients with any grade of alopecia, amenorrhea, grade 2 neuropathy, or other toxicities not considered a safety risk for the patient as per investigator's discretion, are allowed to enter the trial.**	Yes	Yes	Previously, additional toxicities not considered a safety risk for the patient by the investigator may previously have excluded the patient from the study. If an EXCL08 PD was raised for a toxicity that was not deemed to be a safety risk by the investigator, it may be downgraded. This change was made to align with the protocol standard language for ribociclib.
TRT06	Patient was given different treatment then originally randomized to.	This refers for instance when ribociclib is given to a control arm patient ~~or goserelin to a post-meno~~. It will not be considered a deviation: - if site's stock was used instead of centrally-supplied IP for any reason, - if an "incorrect" kit number was delivered to the patient (as long as the correct drug was dispensed) - if goserelin was manually dispensed to a premenopausal patient because of incorrect stratification	Yes	Yes	Previously a post-menopausal patient receiving goserelin would have been considered a PD. However, this criterion was subsequently removed to separate issues where ribociclib is administered to a control arm patient from cases where goserelin is administered to a post-menopausal patient. Initially a new PD code was planned to specifically cover cases of goserelin being administered to a post-menopausal patient. However, last patient first treatment had already occurred, and it was ultimately deemed unnecessary to create a new PD code for this as further stratification errors were unlikely.

*Strikethrough illustrates removed text, bold illustrates newly added text

Source: Applicant's IR response dated March 29, 2024

At Site 1810, there were 3 issues that were downgraded to a non-protocol deviation issue

manually identified by the Applicant:

Issue ID	Issue Description per CTMS extract	Reason for downgrading
IM23992	/TRT06/ Patient was given different treatment than originally randomized to Patient (b) (6) Post menopausal patient received Goserelin. Her status at the beginning was wrongly assessed as premenopausal. After (b) query and deeper investigation status was changed to postmenopausal and goserelin was stopped. New information (b) discussed this issue with PI. Re training was performed on 23Feb2022.Training Log was completed accordingly. PI and SIs are aware on status of patients. As per IA3 on Feb2023 and regarding Appendix I, with the guidance, and it seems that INITIALLY it was expected to report Goserelin given to a Post-menopausal patient as a TRT06 PD, but this was then corrected in a subsequent version. Therefore, this would mean (b) (6) issue should be updated to NON-PD issues/Non COVID-19	Due to revision of TRT06 criteria per TWI
IM24837	/OTH23/Re-onsent process not followed correctly. Patient (b) (6) has not signed ICF v. 5.0 yet apart visit performed on (b) (6). Post Visit note Dr Budny informed (b) that PICF was found and it was signed on the (b) (6) not verified because found after the visit. (b) verified during monitoring visit on (b) (6) - (b) (6) and confirmed that patient signed ICF v. 5.0 on (b) (6). PI was re trained in ICF obtaining process/Non COVID-19	Not a PD issue as the ICF was retrieved and signed in a timely manner.
IM24827	/OTH23/Re-consent process not followed correctly. (b) (6) has not signed ICF v. 5.0 yet apart visit performed on (b) (6). Post Visit note - Dr. Budny informed (b) that ICF was found it was signed on the (b) (6), not verified because happened after the visit. (b) verified and confirmed that patient signed ICF v. 5.0 on (b) (6). PI was re-trained on ICF obtaining process. New information - (b) discussed this issue with PI, SIs and SCs during MV. Re-training was performed on (b) (6). Training Log was completed accordingly. PI, SIs and SCs are aware on 30-Day Post Ribociclib Safety Follow-up and Follow up visits./Non COVID-19	Not a PD issue as the ICF was retrieved and signed in a timely manner.

Source: Applicant's IR response dated March 29, 2024

FDA reviewed these descriptions and agreed with the Applicant that these are unlikely to impact efficacy or safety.

At Site 1811, there were two participants enrolled and randomized despite not meeting eligibility criteria. One participant had a magnesium level that was slightly below the LLN without repeat testing to confirm the result was in range. The other participant was missing ALT results from screening. At the next visit, the ALT was determined to be <2.5 x ULN. Both were reported as protocol violations. Both participants remained on study. There was no apparent harm from their inclusion.

At Site 5007, a total of three AEs in two participants were unreported, one vaginal infection and one viral respiratory infection with a subsequent test positive for SARS-CoV-2. Neither of these were SAEs. Underreporting of these AEs would not alter the assessment of safety for ribociclib in the NATALEE trial in the context of other AE reporting in the NATALEE trial and the current USPI.

Overall, there was no evidence of discrepancy in iDFS events reported at the five inspected trial sites. There was no other evidence of underreporting of AEs at the five inspected trial sites. No significant discrepancies or notable findings were identified at Site 5057 and 5075.

OSI concluded overall that the study appears to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of this sNDA. FDA concurs with OSI's assessment. The review team concluded that the issues identified during inspection do not meaningfully alter the finding of a favorable benefit-risk assessment or preclude regulatory approval.

Refer to the FDA OSI review and FDA correspondence with the Applicant for full details.

4.2 Product Quality

The FDA's Assessment:

The Office of Pharmaceutical Quality (OPQ), CDER recommends approval of these applications for 209092/S-018 and 209935/S-027. Refer to FDA Product Quality's review for full details.

4.3 Clinical Microbiology

The FDA's Assessment:

Not applicable.

4.4 Devices and Companion Diagnostic Issues

The FDA's Assessment:

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The Applicant's Position:
No new information is provided in the current submission for non-clinical pharmacology/toxicology.

The FDA's Assessment:

FDA disagrees that no new information was provided with the sNDA submission. During the review, the Applicant provided results of a GLP enhanced Ames test (EAT) and a GLP in vivo mutagenicity study in Muta™Mice. The Applicant conducted these studies to assess the mutagenic potential of the nitrosamine impurity (b) (4) in support of the proposed ribociclib indication in patients with early breast cancer.

In the GLP EAT using the pre-incubation method, (b) (4) was not mutagenic in *Salmonella typhimurium* strains (TA98, TA100, TA1535, and TA1537) and *Escherichia coli* strain WP2 uvrA pKM101 at concentrations up to (b) (4) µg/plate (the maximum concentration due to limited solubility in vehicle) in the presence or absence of metabolic activation with 30% rat or hamster S9. The standard positive controls for an Ames test and two nitrosamine positive controls (b) (4) showed expected mutagenicity results in the assay.

The Applicant conducted the GLP in vivo mutagenicity study to assess the potential of (b) (4) to induce gene mutation in the lacZ transgene in the liver, duodenum, kidney, and bone marrow in Muta™Mice. The bone marrow and liver are expected to have high exposure to (b) (4). The duodenum is a site of contact tissue following oral gavage dosing, and the kidney is a standard target organ for tumor for nitrosamines.

In the in vivo study, males received doses of 25, 50, and 100/80 mg/kg/day (b) (4), and females received 100 mg/kg/day (b) (4) for 28 days. Due to toxicity and mortalities, the high dose in males was reduced to 80 mg/kg/day on Day 4. (b) (4) induced a statistically significant increase in mutation frequencies (MF) in the lacZ transgene in the duodenum and liver of male Muta™Mice at ≥ (b) (4) mg/kg/day and in the duodenum of female Muta™Mice at (b) (4) mg/kg/day when compared to vehicle controls. The study was validated by the positive results of target tissue samples collected from Muta™Mice treated with (b) (4) a positive control) and the laboratory's historical control data.

Table 2: (b) (4)-Induced Increase in MF in Duodenum of Male Muta™Mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
1	Vehicle control	0	(b) (4)		
2	(b) (4)	25			
3		50			
4		100/80†			
N/A	Positive Control	50			

Dose response (Group 1, 2, 3, 4): P = (b) (4)

† Dose level reduced to 80 mg/kg/day as of Day 4 of dosing due to mortality/morbidity.

Source: Excerpted from the Applicant's submission

Table 3: (b) (4)-Induced Increase in MF in Duodenum of Female Muta™Mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
5	Vehicle control	0	(b) (4)		
6	(b) (4)	100			
N/A	Positive Control	50			

Source: Excerpted from the Applicant's submission

Table 4: (b) (4)-Induced Increase in MF in Livers of Male Muta™Mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
1	Vehicle control	0	(b) (4)		
2	(b) (4)	25			
3		50			
4		100/80†			
N/A	Positive Control	50			

Dose response (Group 1, 2, 3, 4): P = (b) (4)

† Dose level reduced to 80 mg/kg/day as of Day 4 of dosing due to mortality/morbidity.

Source: Excerpted from the Applicant's submission

(b) (4) induced a small but statistically significant increase in MF in the livers of female Muta™Mice at (b) (4) mg/kg/day. All livers of individual Muta™Mice had group mean MF that fell within the 95% negative control range of the laboratory's historical control data except for two female Muta™Mice at (b) (4) mg/kg/day with liver MF slightly above the 95% negative control range. Therefore, the mutagenic effect of (b) (4) in the livers of female Muta™Mice is considered equivocal.

Table 5: Equivocal Increase in MF in Livers of Female Muta™Mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
5	Vehicle control	0	(b) (4)		
6	(b) (4)	100			
N/A	Positive Control	50			

Source: Excerpted from the Applicant's submission

Due to the positive results in the in vivo mutagenicity study, the Applicant followed recommendations in the FDA guidance *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities.* Using quantitative structure-activity relationship analysis and the Carcinogenic Potency Categorization Approach, the CDER Computational Toxicology team confirmed that (b) (4) is assigned to Potency Category 3 with an acceptable intake (AI) of (b) (4) ng/day. The Applicant will ensure (b) (4) is within the AI limit of (b) (4) ng/day for all patients with breast cancer.

The nonclinical data submitted to this sNDA are adequate to support approval of ribociclib in the proposed indication.

Given the chronic use and patient population that includes patients with long-life expectancy, the Applicant previously submitted results of a 2-year carcinogenicity study in rats to assess the carcinogenic potential of ribociclib. The Executive Carcinogenicity Assessment Committee concluded that the study was negative and there was no clear evidence of ribociclib-related neoplasms in rats. The pharmacology/toxicology team recommends a post-marketing requirement to conduct a second GLP carcinogenicity study in mice to further assess the carcinogenic potential of ribociclib.

X	X
George Chang, PhD Primary Non-clinical Reviewer	Tiffany Ricks, PhD Non-clinical Team Lead

6. Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The Applicant submitted NDA 209092 S-018 (ribociclib) and NDA 209935 S-027 (ribociclib and letrozole co-pack) to seek approval for a new indication of:

(b) (4)

Selection of the ribociclib dose and regimen (400 mg/day, on Days 1 to 21 days of a 28-day cycle for 3 years) was based on post-hoc exploratory analyses from the MONALEESA-2, 3, and 7 programs using previous PK-QTcF and ANC exposure-response (E-R) modeling of data, exposure-efficacy analysis, exploratory progression-free survival (PFS) analysis in patients with advanced or metastatic breast cancer (aBC), and data on the long-term use of ribociclib in aBC patients to support the extended duration of treatment.

In the adjuvant trial (NATALEE), the primary efficacy endpoint of iDFS was statistically significant with an acceptable safety profile compared to ET alone and with an improved safety profile when compared to that in aBC patients receiving ribociclib 600 mg QD plus ET.

The E-R analysis for efficacy is considered exploratory due to limited PK data collected in the pivotal trial in patients with eBC. The popPK analyses indicates the impact of hepatic and renal impairment on the PK of ribociclib in patients with eBC was similar to that in patients with aBC. The predications by updated physiologically based pharmacokinetic (PBPK) model of ribociclib are consistent with conclusions and DDI management strategies from the original NDA submission and are applicable to both aBC and eBC patient populations.

FDA Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in NDA 209092 S-018 and NDA 209935 S-027 and determined the submissions are approvable from a clinical pharmacology perspective.

Table 6: Key Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive	The primary evidence of effectiveness is the statistically significant improvement in iDFS at interim analysis 3 (IA3) when patients were

evidence of effectiveness	**administered ET plus ribociclib compared to ET alone from the pivotal NATALEE trial (See Section 8.1.5).** **The E-R analysis for efficacy is considered exploratory due to limited PK data collected in the pivotal NATALEE trial (See Section 19.4.2.4).**
General dosing instructions	**The proposed recommended dosage is 400 mg ribociclib daily, on Days 1 to 21 days of a 28-day cycle. This is a lower starting dosage than the 600 mg dosage recommended for advanced or metastatic breast cancer (aBC).** **Median relative dose intensity in eBC patients receiving ribociclib 400 mg dosage plus ET was 94%; and dose reductions, and discontinuations were improved when compared to aBC patients receiving ribociclib 600 mg dosage plus ET. Both neutropenia and QTcF prolongation, which have a known concentration-dependent relationship, were lower in eBC patients in the NATALEE trial at the dosage of 400 mg than in aBC patients at the dosage of 600 mg, supporting improved tolerability of the 400 mg dosage in eBC patients. Refer to Section 8.2.5.1.**
Dosing in patient subgroups	**1. No therapeutic individualization of ribociclib in eBC is needed based upon intrinsic factors such as age, body weight, sex, or race and no new intrinsic factors were identified for dose adjustment.** **2. The popPK analysis indicated the impact of hepatic and renal impairment on the PK of ribociclib in patients with eBC was similar to that in patients with aBC.**
Drug-drug interactions	**No additional clinical drug-drug interaction studies were conducted with ribociclib. A PBPK model for ribociclib was updated to support dosage recommendations for concomitant strong CYP3A4 inhibitors and moderate CYP3A4 inhibitors and inducers. For 400 mg and 600 mg dosages of ribociclib, the PBPK model predicted the following:** **• Ritonavir (strong CYP3A4 inhibitor) increases ribociclib steady state AUC by 1.8-fold and 1.6-fold, respectively.** **• Erythromycin (moderate CYP3A4 inhibitor) increases ribociclib steady state AUC by 1.2-fold and 1.1-fold, respectively.** **• Efavirenz (moderate CYP3A4 inducer) decreases ribociclib steady state Cmax by 55% and AUC by 74% following 400 mg dosage, and 52% and 71%, respectively following ribociclib 600 mg dosage.**

Labeling	**The proposed labelling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the draft label.**

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of ribociclib has been well characterized and results were submitted in the initial New Drug Application (#209092) and supplemental NDA. The data in the original submission included data of single-dose pharmacokinetics (PK) in healthy subjects, multiple-dose PK in patients with advanced solid tumors, including patients with HR-positive, HER2-negative aBC, mass balance (absorption, distribution, metabolism, and excretion), drug-drug interactions (DDIs), exposure-response/safety relationships, bioequivalence and relative bioavailability of formulations, cardiac safety, food effects on PK, PK in special populations (hepatic and renal impairment), and population PK in patients. Refer to the original NDA submission for ribociclib PK characterization.

The supplemental NDA included clinical pharmacology data supporting the proposed dose regimen in the general population, PK characterization in special populations (moderate/severe hepatic and severe renal impairment) and the dose recommendation, updated population PK in patients, updated food-drug interaction, and DDI with combination partners.

The current supplemental NDA includes clinical pharmacology data primarily comprising of pharmacokinetic (PK) data from the pivotal Study CLEE011O12301C (hereafter Study O12301C) in patients with eBC, and Study CLEE011A2207 (AMALEE) (hereafter Study A2207) in patients with aBC. [Study O12301C Primary Analysis CSR] is a Phase III, randomized, open-label study to evaluate the effect of the addition of 400 mg ribociclib to standard adjuvant endocrine therapy (non-steroidal aromatase inhibitor (NSAI); anastrozole or letrozole) in the treatment of pre- and postmenopausal women, plus men, with HR-positive, HER2-negative, eBC. [Study A2207 Primary Analysis CSR] is a Phase II, randomized, open-label study to evaluate the safety and efficacy of 400 mg and 600 mg ribociclib in combination with NSAIs in the treatment of pre- and postmenopausal women with HR-positive, HER2-negative aBC.

In addition, updated population PK (popPK) analysis using Study O12301C data, comparison of PK data of Study O12301C and historical studies, updated PK-QT analysis of pooled clinical data, exposure-efficacy, exposure-neutropenia analyses of Study O12301C, and the updated assessment of drug-drug interaction (DDI) and subpopulation PK in patients with renal and/or liver impairment at the dose of 400 mg are also presented.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. See Section 6.3 for FDA's summary of general clinical pharmacology and PK characteristics of ribociclib.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

The pivotal Phase III study O12301C evaluated ribociclib 400 mg for eBC patients. Selection of the ribociclib dose and regimen (400 mg daily on Days 1 to 21 of a 28-day cycle) was based on previous PK-QTcF and ANC exposure-response modeling of data in patients with advanced cancer, exposure-efficacy analysis, and exploratory progression-free survival (PFS) analysis by dose reduction in patients with aBC. Results of Study O12301C demonstrated that the 400 mg ribociclib dose is safe and efficacious for use for eBC. Thus, the recommended dose of ribociclib for the adjuvant setting for eBC is 400 mg (two 200-mg film-coated tablets) of ribociclib once daily, Days 1 to 21 of each 28-day cycle for 3 years combined with 5 years of ET.

The FDA's Assessment:

FDA generally agrees with the Applicant. The proposed recommended ribociclib dosage of 400 mg daily, on Days 1 to 21 of a 28-day cycle is acceptable for the indicated eBC patient population as it is supported by the efficacy and safety demonstrated in patients with eBC enrolled in the pivotal NATALEE trial. Refer to Section 6.3 for data and analyses supporting the proposed dosing regimen.

6.2.2.2 Therapeutic Individualization

The Applicant's Position:

Specific populations: The recommendation for alternative dosing regimen for subpopulations based on intrinsic patient factors has no change since the prior approvals [Studies E2301/F2301].

Patients with hepatic impairment: In Study O12301C, no apparent increase in exposure was observed in patients with mild hepatic impairment, however, the sample size is limited (n=9). A total of 3 patients with moderate hepatic impairment were treated in the ribociclib arm of Study O12301C. Based on the data in eBC patients, the previously submitted hepatic impairment data in non-cancer subjects and advanced cancer patients, as well as post-marketing experience in aBC patients, no ribociclib dose adjustment is warranted for eBC patients with hepatic impairment [SCP Study O12301C-Section 5.2.1].

Patients with renal impairment: In Study O12301C, there was no apparent effect of mild renal impairment on ribociclib PK exposure. No apparent increase in exposure was observed in patients with moderate renal impairment, however, the sample size is limited (n=8). Based on the data in eBC patients and the previously submitted renal impairment data in aBC patients and non-cancer subjects, no dose reduction is required for eBC patients with mild or moderate renal impairment, and a lower starting dose of 200 mg is recommended in eBC patients with severe renal impairment [SCP Study O12301C-Section 5.2.2].

Drug-drug interactions:

Effect of concomitant-medications on ribociclib: PBPK model-predicted ribociclib steady-state Cmax and AUC ratios with vs without coadministration of ritonavir were 1.47 and 1.84, respectively, in patients with eBC at the dose of 400 mg. Alternate concomitant medication with a low potential to inhibit CYP3A should be considered in eBC patients. If co-administration of ribociclib with a strong CYP3A inhibitor cannot be avoided, monitor for adverse reactions and consider reducing the dose to 200 mg, if necessary.

Rifampicin (a strong CYP3A4 inducer) decreased ribociclib Cmax and AUCinf by 81% and 89%, respectively, following a single oral dose of 600 mg ribociclib, compared to ribociclib alone in Study A2101 [SCP Study A2301]. Concomitant use of ribociclib with strong CYP3A4 inducers should be avoided in patients with eBC [SCP Study O12301C-Section 5.3.1].

Effect of ribociclib on concomitant medications: Ribociclib dosed at 400 mg once daily is a moderate inhibitor of CYP3A4 and increased steady-state exposure of the CYP3A4 substrate midazolam by 280% (3.8-fold). Caution is recommended when ribociclib 400 mg is administered with CYP3A substrates with a narrow therapeutic index in patients with eBC. The dose of a sensitive CYP3A substrate with a narrow therapeutic index may need to be reduced.

Based on in vitro inhibition data at the dose of 400 mg dose, ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations [SCP Study O12301C-Section 5.3.2].

The FDA's Assessment:

FDA agrees with the Applicant's position that no therapeutic individualization of ribociclib is needed based upon intrinsic factors from the popPK modeling results including age, body weight, sex, or race. The impact of renal and hepatic impairment on the PK of ribociclib in patients with eBC was similar to that in patients with aBC. No new intrinsic factors were identified for dose adjustment. Refer to Section 6.3.2.3.

For patients with eBC, the FDA agrees with dose reduction from 400 mg QD to 200 mg QD when co-administration of a strong CYP3A4 inhibitor, based on PBPK predictions. Co-administration of moderate CYP3A4 inhibitor is not expected to meaningfully change the exposure of ribociclib at steady state. A moderate effect is expected with co-administration of a moderate CYP3A4 inducer. For patients with aBC, PBPK predictions, using the updated model of ribociclib, are consistent with conclusions and DDI management strategies from the original NDA submission. Refer to section 19.4.3 for details about the PBPK modeling analysis.

6.2.2.3 Outstanding Issues

The Applicant's Position:
There are no PMR/PMCs currently ongoing.

The FDA's Assessment:

FDA concurs with the Applicant's position.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Comprehensive PK data on ribociclib were provided in the prior submissions.

In Study O12301C in patients with eBC, the population mean estimate of the apparent clearance of ribociclib in eBC patients was 38.4 L/hr at a 400 mg dose, based on population PK modeling. In Study A2207 in patients with aBC, the geometric mean Cmax and AUC0-24h were approximately 28% and 43% lower for the ribociclib 400 mg arm as compared to the ribociclib 600 mg arm. The observed geometric mean apparent clearance at steady-state was 24.4 L/hr at 400 mg and 21.0 L/hr at 600 mg in patients with aBC.

The steady-state PK exposure in eBC patients in Study O12301C at 400 mg was lower than those in advanced cancer patients in Study X2101 at the dose of 600 mg (56% and 48% lower for AUC and Cmax, respectively), which can be attributed to lower dose as well as faster clearance due to PK nonlinearity and population effect potentially due to no detectable disease in eBC patients [CO Study O12301-Section 3.1.2].

The FDA's Assessment:

FDA generally agrees with the Applicant on the general clinical pharmacology characteristics of ribociclib. The updated popPK model adequately characterized the PK profile of ribociclib in patients with eBC who received the proposed recommended dosage. Refer to Section 19.4.1 for data and analyses related to popPK modelling.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. Collectively, the clinical pharmacology program supports the use of ribociclib 400 mg in combination with ET (letrozole or anastrozole) in patients with HR-positive, HER2-negative eBC. Selection of the ribociclib dose and regimen (400 mg daily on Days 1 to 21 of a 28-day cycle) is discussed in Section 6.2.2.1.

The evidence of effectiveness of ribociclib was demonstrated in Study O12301C in patients ≥ 18 years of age with HR-positive, HER2-negative, Stage II or Stage III eBC by the statistically significant improvement of both the primary endpoint of iDFS and the secondary endpoints of RFS and DDFS. Detailed efficacy results are provided in Section 8.1.2.

Due to limited sample size of patients with iDFS events, exposure-efficacy relationship cannot be characterized [CO Study O12301C-Section 3.3].

The FDA's Assessment:

FDA agrees that effectiveness of the proposed recommended dosage of ribociclib 400 mg daily for Days 1 to 21 days in a 28-day cycle with ET was demonstrated via the primary endpoint of iDFS in the NATALEE trial (See Section 8.1.5). The exposure-efficacy relationship is considered exploratory and could not be adequately characterized due to the limited PK data collected in the NATALEE trial. Refer to Section 19.4.2 for data and analyses regarding the exposure-response relationship between ribociclib exposure and iDFS from the NATALEE trial.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. Based on the observed efficacy and safety data of Study O12301C, exposure-response analysis, and the historical data in patients with aBC, 400 mg ribociclib (once daily for 3 weeks on/1 week off in a 28-day cycle) is demonstrated to be a safe and effective dose in patients with eBC.

Both neutropenia and QTcF prolongation, the adverse events related to ribociclib PK exposure, are lower in eBC patients in Study O12301C at the dose of 400 mg than in aBC patients at the dose of 600 mg, supporting improved tolerability of the 400 mg dose in eBC patients. The PK-QT modeling confirmed the exposure-QTcF relationship in eBC patients, and patient population is a significant covariate where eBC patients showed less QTcF response than aBC patients.

Efficacy in patients with eBC was demonstrated by the statistically significant improvement of both the primary endpoint of iDFS and the secondary endpoints of RFS and DDFS. Due to limited sample size of patients with a PK collection having an iDFS event, the exposure-efficacy relationship cannot be characterized [SCP Study O12301C-Section 5.5].

The FDA's Assessment:

FDA agrees that the recommended dosage of ribociclib 400 mg daily for Days 1 to 21 of a 28-day cycle is appropriate for the general population of adults with HR+, HER2-negative stage II and III eBC based on the primary endpoint of iDFS from the NATALEE trial. The following are the Applicant's rationales for dosage selection for the NATALEE trial:

- **As extended duration of treatment is critical to prolong cell cycle arrest and drive more tumor cells into senescence/death, a 3-year duration of treatment was chosen at a dose of 400 mg to improve tolerability while maintaining efficacy.**
- **There are sufficient safety data on long-term use of ribociclib (> 60 months) in the aBC setting to support the longer treatment duration in the NATALEE trial.**
- **The 400 mg dose was selected based on consistent efficacy in post hoc exploratory analyses from the MONALEESA program, and a potentially improved safety**

profile in terms of dose-dependent toxicities such as QTc prolongation and neutropenia as compared to the 600 mg dosage.

Therefore, this dosage and treatment duration were chosen to optimize efficacy while improving tolerability in this patient population with no detectable disease.

Both neutropenia and QTcF prolongation, which have a known concentration-dependent relationship, were less common in the NATALEE trial at the dosage of 400 mg than in trials in the advanced setting at the dosage of 600 mg, supporting improved tolerability of the 400 mg dosage in patients with eBC.

The median relative dose intensity for eBC patients receiving 400 mg dosage plus ET (compared to aBC patients receiving the 600 mg dosage) was 94% (vs 87.5%), while dose reductions (due to AEs) was 23.1% (vs 45%), and discontinuations was 19.7% (vs 15%). In general, the lower recommended dosage in eBC demonstrated greater tolerability compared to patients with aBC receiving 600 mg dosage plus ET as reported in the most recent USPI.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:
Yes. The recommendation for alternative dosing regimen for subpopulation based on intrinsic patient factors has no change since the prior approvals [Studies E2301/F2301].

Intrinsic factors: No clinically relevant effects of age, body weight (BW), gender, or race on the systemic exposure of ribociclib in the adult population that would require a dose adjustment were identified based on the popPK analysis previously submitted [Study A2301], [Studies E2301/F2301] [SCP Study O12301C-Section 1.1.1.2.1]. No new information is submitted in this application.

Details on patients with hepatic and renal impairment are provided in Section 6.2.2.2.

The FDA's Assessment:

FDA agrees that no therapeutic individualization of ribociclib is needed based upon intrinsic factors from the popPK modeling results including age, body weight, sex, or race. Additionally, no new intrinsic factors were identified for dose adjustment in this application.

There are limited data for hepatic impairment in the NATALEE trial: 9 patients with mild hepatic impairment and 3 patients with moderate hepatic impairment in which no PK data were available. Patients with severe hepatic impairment were excluded from the trial. Based upon data from the most recent USPI, moderate hepatic impairment increased ribociclib exposure (GMR) by 1.4 for C_{max} and 1.3 for AUC_{inf}, while severe hepatic

impairment increased ribociclib exposure by 1.3 for both C_{max} and AUC_{inf}. The Applicant is proposing no dose adjustments for patients with mild and moderate hepatic impairment, which is the same recommendation for patients with aBC.

There are similar limited data for moderate renal impairment. In the NATALEE trial, 42 patients had mild renal impairment and 8 patients had moderate renal impairment. Patients with severe renal impairment were excluded from the NATALEE trial. Based upon data from the most recent USPI, severe renal impairment increased ribociclib exposure (GMR) by 2.7 for C_{max} and 2.1 for AUC_{inf}. The Applicant is proposing no dose adjustment for mild or moderate renal impairment, and a dose reduction to 200 mg QD (50% dose reduction) for patients with severe renal impairment.

Despite these limitations, the Applicant's proposed dosing for eBC patients with renal and hepatic impairment are acceptable. Based on the popPK model, the impact of renal and hepatic impairment on the PK of ribociclib in patients with eBC was similar to that in patients with aBC. Because the benefit-risk profile of these subpopulations has been established in patients with aBC receiving the higher 600 mg dosage, patients with eBC who have mild to moderate hepatic impairment or severe renal impairment receiving the lower recommended dose of 400 mg are not expected to experience unacceptably high ribociclib exposures leading to additional safety concerns.

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

The Applicant's Position:
No new information for food-drug interactions is provided in this submission. Details on patients with drug-drug interactions and the management strategy are provided in Section 6.2.2.2.

The FDA's Assessment:

FDA agrees that no new information for food-drug interactions is pertinent to this submission. Assessment about DDI results and management strategy are presented in Section 6.2.2.2.

X	X

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7 Sources of Clinical Data

7.1 Table of Clinical Studies

The Applicant's Position:

Table 7: Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Study to Support Efficacy and Safety						
CLEE011O12301C	NCT03701334	A global, Phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with ET (investigational arm: ribociclib + ET) versus ET alone (control arm: ET only) as adjuvant treatment in patients with HR-positive, HER2-negative, eBC.	Ribociclib 400 mg once daily on Days 1 to 21 of each 28-day cycle (up to 36 months of treatment) ET: letrozole 2.5 mg by mouth, once daily, given continuously or anastrozole 1 mg by mouth, once daily, given continuously (for premenopausal women and men, plus goserelin 3.6 mg subcutaneously, on Day 1 ±3 of each 28-day cycle (up to 60 months of treatment)	**Primary endpoint**: - iDFS using STEEP criteria, as assessed by Investigator. **Secondary endpoints**: - RFS using STEEP criteria DDFS using STEEP criteria - Overall survival - Change from baseline in the physical functioning sub-scale score and global health status / QoL scale score as assessed by EORTC QLQ-C30.	The final iDFS analysis was conducted after 40.3 months of median study follow-up, when patients were treated for a median duration of 36 months in both arms, with an additional 6.3 months of study follow-up from the primary analysis.	Randomized to ribociclib + ET arm: 2549 patients Randomized to ET only arm: 2552 patients	The study population consisted of female and male patients ≥18 years of age (and if female, with a known menopausal status at the time of randomization) with histologically confirmed diagnosis of ER and/or PR-positive, HER2-negative eBC with Anatomic Stage Group	A total of 393 centers across 20 countries

				- Frequency and severity of AEs, laboratory and ECG abnormalities. - PK parameters such as C_{trough} and other applicable parameters for ribociclib **Exploratory endpoints**: - LRRFS defined as time from date of randomization to date of first event of local invasive breast recurrence, regional invasive recurrence, or death due to any cause. - Incidence of subsequent anti-neoplastic therapy and time to first subsequent anti-neoplastic therapy. - Number of patients hospitalized, total number of hospitalizations, and length of stay in hospitals, number of patients with Emergency Room and additional visits.			III, IIB, or a subset of IIA cases, after adequate surgical resection, radiotherapy (if indicated), adjuvant or neoadjuvant chemotherapy (if indicated), and who were deemed eligible for adjuvant ET for at least a 60-month duration. Stage IIA patients with no nodal involvement had either tumor grade 3 or tumor grade 2 with high-risk genomic profile or Ki67 ≥20%.	

The FDA's Assessment:

For the sNDA, the Applicant submitted the results from the NATALEE trial in patients with high-risk Stage II or III HR+, HER2-negative early breast cancer comparing ribociclib + ET to ET only in the adjuvant setting. FDA generally agrees with the Applicant's description of the design of the NATALEE trial above.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study CLEE011O12301C

Trial Design

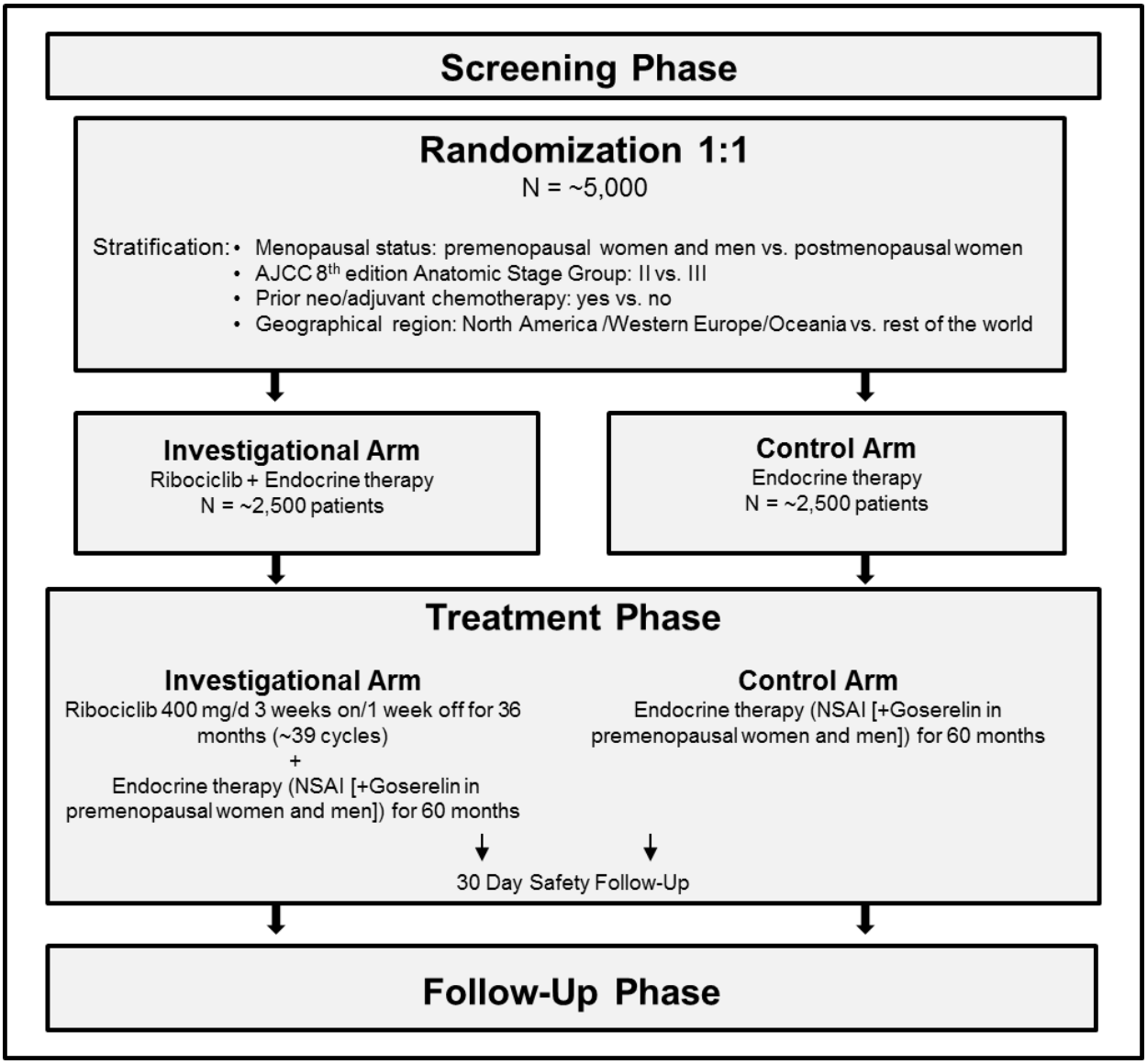
The Applicant's Description:

Study CLEE011O12301C is a Phase III, multicenter, randomized, open-label study to evaluate the efficacy and safety of ribociclib with ET versus ET alone as an adjuvant treatment in pre- and postmenopausal women plus men with HR-positive, HER2-negative eBC.

Approximately 5,000 patients were planned to be randomized (using an IRT system) in a 1:1 ratio to either the investigational arm (ribociclib + ET) or the control arm (ET only). Randomization to the two treatment arms was stratified by menopausal status (premenopausal women, and men vs. postmenopausal women), AJCC 8th edition Stage II vs. Stage III, prior neoadjuvant/adjuvant chemotherapy (yes vs. no), and Geographical region (North America/Western Europe/Oceania vs. rest of the world). The planned study treatment phase duration was 60 months.

In total, 5101 female and male patients were randomized in a 1:1 ratio; 2549 patients to the ribociclib + ET arm and 2552 patients to the ET only arm (Figure 1: Study design).

Figure 1: Study design



The FDA's Assessment:

FDA generally agrees with the Applicant's description of the design of the NATALEE trial. Letrozole and anastrozole were used as endocrine therapy in NATALEE, due to the following reasons provided by the Applicant in an IR response from Sept 9, 2024:

- ***Exemestane was not excluded explicitly in the protocol as safety and efficacy data have been generated in combination of ribociclib and exemestane in the metastatic disease setting.***

- ***The AROMASIN (exemestane) indication for adjuvant treatment is as follows: adjuvant treatment of postmenopausal women with estrogen-receptor positive eBC who have received two or three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy.***
- ***Therefore, given the protocol eligibility criteria for prior ET duration of up to 1 year, patients eligible to receive exemestane would have had to receive at least 2 years of prior tamoxifen, thus becoming ineligible for NATALEE***
- ***From a purely practical and operational perspective, and in light of the above, only anastrozole or letrozole were made available.***

The rationale for primarily using letrozole and anastrozole in the NATALEE trial is reasonable for the reasons outlined by the Applicant, and does not impact the overall benefit-risk assessment.

Eligibility Criteria

The Applicant's Description:

The pivotal study O12301C supporting this submission has participation across all demographic patient populations and included patients of diverse race and ethnicities with the majority of patients being White (73.4%) and not of Hispanic or Latino origin (81.0%). Details are presented in Table 10: Demographic Characteristics. The study population consisted of female and male patients ≥18 years of age (and if female, with a known menopausal status at the time of randomization) with histologically confirmed diagnosis of ER and/or PgR-positive, HER2-negative eBC with Anatomic Stage Group III, IIB, or a subset of IIA cases, after adequate surgical resection, radiotherapy (if indicated), adjuvant or neoadjuvant chemotherapy (if indicated), and who were deemed eligible for adjuvant ET for at least a 60-month duration. Stage IIA patients with no nodal involvement had either tumor grade 3 or tumor grade 2 with high-risk genomic profile or Ki67 ≥20%. In general, the patients enrolled in this study were representative of the intended target patient population and allow the resultant data to be extrapolated to all patients with the proposed indication. Detailed demographic and baseline characteristics are discussed in Section 8.1.2.

Trial location

393 sites across 20 countries in Europe, North America/Australia, Asia, and Latin America enrolled a total of 5101 patients [Study O12301C Primary Analysis CSR-Section 2].

Choice of control group

The choice of control treatment (ET) was based on its recommended use as a standard of care in patients with ER-positive eBC. Another consideration behind the choice of ET for this study was the fact that, as per the Kisqali® prescribing information, ribociclib is not indicated for use in combination with tamoxifen due to the increased risk of QT prolongation. Hence, for this study, patients in the control arm were treated with standard AI, either letrozole or anastrozole, administered for a duration of at least 60 months from randomization, according to the local

clinical guidelines and current prescribing information. Gonadal suppression was achieved by using the GnRH agonist goserelin [CO Study O12301C-Section 1.3.2].

Diagnostic criteria

The study population had histologically confirmed diagnosis of ER and/or PgR-positive, HER2-negative breast cancer within 18 months prior to randomization. Patients with histologically confirmed unilateral primary invasive adenocarcinoma of the breast with a date of initial cytologic or histologic diagnosis within 18 months prior to randomization were included. Patients with a multicentric and/or multifocal tumor were eligible if all the histopathologically examined lesions met the pathologic inclusion criteria [Study O12301C Primary analysis CSR-Section 9.3.1]

In the United States, breast cancer is projected to be the most common cancer diagnosed in 2023 with an estimated incidence of 297,790 new cases and 43,170 deaths (SEER 2023). Almost all newly diagnosed BC cases are early BC (eBC), localized to the breast tissue and regional lymphatics, which are potentially curable with surgical resection and a variety of treatment modalities. Based on SEER Program data collected between the years 2010 and 2019, among all HR-positive, HER2-negative breast cancer cases in females, 94.8% of cases diagnosed were eBC, with 68.9% localized to the breast tissue and 25.9% within both the breast tissue and regional lymph nodes (SEER 2022) [CO Study O12301-Section 1.1].

Key inclusion/exclusion criteria

The study population consisted of female and male patients ≥ 18 years of age (and if female with a known menopausal status at the time of randomization) with HR-positive, HER2-negative eBC. Patients were included if they had a histologically confirmed diagnosis of ER and/or PgR positive (HR-positive), HER2-negative eBC (Anatomic Stage Group III, IIB, IIA), irrespective of nodal status, after adequate surgical resection and radiotherapy (if indicated), within 18 months prior to randomization and who were deemed eligible for adjuvant ET for at least a 60-month duration. Patient may have already received any standard neoadjuvant and/or adjuvant ET at the time of informed consent, but randomization was to occur within 12 months of the initial start date of ET. Note, Stage IIA patients who were node negative were required to have either tumor grade 3 or tumor grade 2 with high risk genomic profile or Ki67 ≥ 20%. Eligible patients were also required to have adequate bone marrow and organ function as defined in the Study Protocol, and standard 12-lead ECG values assessed by a central laboratory.

Key exclusion criteria included prior treatment with any CDK4/6 inhibitor; tamoxifen, raloxifene or AIs for chemoprevention of breast cancer and/or treatment for osteoporosis (within 2 years of randomization); anthracyclines (specified doses of doxorubicin and epirubicin); and systemic corticosteroids (within 2 weeks of starting trial treatment). Patients receiving treatment with any other antineoplastic therapy (except for adjuvant ET) were not eligible. Patients with breast cancer metastases beyond regional lymph nodes (Stage IV according to AJCC 8th edition) and/or evidence of recurrence after curative surgery; patients who had major surgery, chemotherapy, or radiotherapy (within 14 days of randomization); patients with a known hypersensitivity to any of the excipients of ribociclib and/or ET; and patients with clinically significant, uncontrolled heart

disease and/or cardiac repolarization abnormality were excluded [Study O12301C-Section 2 synopsis].

Dose selection

As extended duration of treatment is critical to prolong cell cycle arrest and drive more tumor cells into senescence/death, a 3-year duration of treatment was chosen at a dose of 400 mg to improve tolerability while maintaining efficacy. Of note, there are sufficient safety data on long-term use of ribociclib (> 60 months) in the aBC setting to support the longer treatment duration in Study O12301C. The 400 mg dose was selected based on consistent efficacy in post hoc exploratory analyses from the MONALEESA program, and a potentially improved safety profile in terms of dose-dependent toxicities such as QTc prolongation and neutropenia as compared to the 600 mg starting dose. Therefore, this dose and treatment duration were chosen to optimize efficacy while improving tolerability in this patient population with no detectable disease [SCE Study O12301C-Section 4.1].

Study treatments, assignment, and blinding

Ribociclib, the investigational drug for this study, was considered an IMP. The other drugs used in this study were NSAIs (letrozole or anastrozole) and goserelin. Ribociclib was administered orally on a 28-day cycle; on Days 1 to 21 at a dose of 400 mg (two 200 mg film-coated tablets once daily), followed by 7 days off ribociclib (days 22 to 28). ET was administered (in both the investigational and control arms) as follows: for postmenopausal women, letrozole 2.5 mg (orally) once daily and continuously or anastrozole 1 mg (orally) once daily and continuously; for premenopausal women and men, letrozole 2.5 mg (orally) once daily and continuously or anastrozole 1 mg (orally) once daily and continuously, combined with goserelin 3.6 mg (subcutaneously) once every 4 weeks [Study O12301C Primary analysis CSR-Section 2].

Patients were randomized via IRT to the investigational or control arm, in a ratio of 1:1, as per the stratification factors.

Although this is an open-label study, to minimize bias during data review, the study team was blinded to aggregate reports by treatment arm until the time of the final iDFS analysis (or until after interim iDFS analysis if futility or superiority was declared). At the time of interim analyses for iDFS, unblinded results from the interim analyses were not communicated to the Novartis clinical team or to any party involved in the study conduct (apart from the independent statistician and DMC members) until the DMC had determined that either (i) iDFS analysis had crossed the pre-specified boundary for efficacy, or (ii) the study needed to be terminated due to any cause including futility or safety reasons [Study O12301C Primary analysis CSR-Sections 9.4.1 and 9.4.3].

Dose modification, dose discontinuation

Investigators were permitted to interrupt and/or reduce the ribociclib dose to allow patients to continue treatment. Dose modifications were considered for patients who did not tolerate the protocol-specified dosing schedule for ribociclib or where clinical judgment of the treating physician determined that ribociclib dose interruptions and/or reductions were recommended

(based on the individual benefit/risk assessment). For patients who did not tolerate the protocol-specified dosing schedule, one dose reduction was permitted to allow patients to continue ribociclib. If a second dose reduction was required to manage ribociclib-related AEs, then ribociclib was discontinued. No dose re-escalation was permitted.

ET-related AEs were managed according to local clinical guidelines and Investigators' judgment. In cases when ET required interruption for more than 4 weeks due to ET-related AEs, discussions on the risks/benefits of study treatment continuation were held with the Medical Monitor [Study O12301C Primary analysis CSR-Sections 9.4.4 and 9.4.6]. Discontinuations are discussed in the sections below.

Administrative structure

The administrative structure of the study, including internal and external participants, the list of Investigators, as well as members of the Data Monitoring Committee and Study Steering Committee, is provided in [Study O12301C-Appendix 16.1.4].

Concurrent medications

Medications required to treat AEs, manage cancer symptoms, concurrent diseases, and supportive care agents, such as pain medications, antiemetics and antidiarrheals were allowed. Permitted concomitant therapy included bisphosphonates and denosumab, corticosteroids (topical applications, inhaled sprays, eye drops or local injections or short duration of systemic corticosteroids less than or equal to the anti-inflammatory potency of 4 mg dexamethasone), hematopoietic growth factors, concomitant surgery during Ribociclib treatment 'week-off'.

Medications to be used with caution during ribociclib treatment included medications that carry a possible risk for QT prolongation and/or TdP, moderate inhibitors or inducers of CYP3A4/5, sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index, strong inhibitors of Bile Salt Export Pump, sensitive substrates of the renal transporters, MATE1 and OCT2, and sensitive substrates of transporter of Breast Cancer Resistance Protein.

Prohibited concomitant therapy included strong inhibitors or inducers of CYP3A4/5, substrates of CYP3A4/5 with a narrow therapeutic index, medications with a known risk for QT prolongation and/or TdP, concomitant tamoxifen or toremifene use [Study O12301C Primary analysis CSR-Sections 9.4.5]

Treatment compliance

Patients were instructed on how to take the study treatment as per protocol. Site staff ensured that the patient clearly understood the treatment schedule and that the appropriate dose of study treatment was provided at each cycle. Additionally, patients completed a diary to record their daily intakes. The administration of study treatment was recorded in the appropriate sections of the eCRF. Study treatment compliance was assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the patient and/or caregiver. Patients were instructed to return all unused ribociclib (and ET if provided by Novartis), including all partially used and empty containers, at each visit during the Treatment phase. A record of study

treatment receipt and dispensing was maintained in a drug accountability log which was reviewed by a study monitor during regular site visits. [Study O12301C Primary analysis CSR-Sections 9.4.1 and 9.4.3.4]

Subject completion, discontinuation, or withdrawal

Study completion: If the primary endpoint, iDFS, was statistically significant at the second, third interim or at final analysis, data collection was to continue, and end of study was to be declared when 60 months + 30 days (Safety follow up) have elapsed from the date the last patient has been randomized. [Study O12301C Primary analysis CSR-Sections 9.4.7]

Study discontinuation or withdrawal: The Investigator was obliged to discontinue study treatment for a given patient if he/she believed that continuation would be detrimental to the patient's well-being. In the investigational arm, patients were discontinued from ribociclib treatment for any of the following reasons: completion of 36 months of treatment from the randomization date (approximately 39 cycles), regardless of any treatment interruption, first recurrence (any of the following or combination of local, regional, or distant recurrences, or contralateral invasive BC, or second primary non-breast invasive cancer), adjustments to study treatment due to toxicity that result in treatment discontinuation, ribociclib dosing was interrupted for > 28 days due to ribociclib-related toxicity, withdrawal of consent by the patient, patient is lost to follow-up, death, discontinuation from the study treatment due to any other reason, or Novartis termination of the study. [Study O12301C Primary analysis CSR-Sections 9.4.6]

Censoring pattern of iDFS: Number of patients with an iDFS event and number of patients censored for the iDFS analysis were summarized. In addition, a summary of reasons for iDFS censoring was provided by treatment arm.

For patients without an iDFS event, the iDFS censoring date was determined as the last assessment before the earliest of the following dates, with the earliest of these also determining the censoring reason (as indicated in parentheses):

- Analysis cut-off date (censoring reason: 'Ongoing without event')
- Date of consent withdrawal (censoring reason: 'Withdrew consent')
- Date of Last Contact for patients lost to follow-up at EOT or Date of Visit/contact for patients lost to follow-up during follow-up phase (censoring reason: 'Lost to follow up') [Study O12301C Primary Analysis CSR Appendix 16.1.9-Section 2.5.6]

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the design of the NATALEE trial as stated above.

Analysis sets

The Applicant's Description:

The **Full analysis set (FAS)** comprised all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients were analyzed according to the treatment and strata they had been assigned to during the randomization procedure.

The **Per protocol set (PPS)** consisted of a subset of patients in the FAS who were compliant with requirements of the protocol. Sensitivity analyses of the primary endpoint of iDFS could be performed using data from the PPS if the FAS and PPS differ and if the primary analysis was significant.

The **Safety set** included all randomized patients who received any study treatment (i.e., at least one dose of ribociclib or ET). Patients were analyzed according to the study treatment received.

The actual treatment received corresponded to:

- Ribociclib + ET if patients took at least one dose of ribociclib
- ET if patients took at least one dose of ET but ribociclib was never received

The **Pharmacokinetic analysis set** (PAS) consisted of all patients who provided at least one evaluable PK concentration [Study O12301C Primary Analysis CSR-Section 9.7.2]

Study Endpoints

The Applicant's Description:

Objective	Endpoint
Primary	
To compare iDFS for ribociclib + ET versus ET in patients with HR-positive, HER2-negative, eBC	iDFS using STEEP criteria, as assessed by Investigator
Secondary	
To evaluate the two treatment arms with respect RFS	RFS using STEEP criteria
To evaluate the two treatment arms with respect to DDFS	DDFS using STEEP criteria
To evaluate the two treatment arms with respect to OS	OS defined as time from date of randomization to date of death due to any cause
To evaluate PRO for health-related QoL in the two treatment arms	Change from baseline in the physical functioning sub-scale score and global health status / QoL scale score as assessed by EORTC QLQ-C30
To evaluate safety and tolerability of the treatment regimen	Frequency and severity of AEs, laboratory and Electrocardiogram (ECG) abnormalities
To characterize the PK of ribociclib when given in combination with NSAI (and goserelin if applicable)	PK parameters such as C_{trough} and other applicable parameters for ribociclib
Exploratory	

Objective	Endpoint
To explore the two treatment arms with respect to LRRFS	LRRFS defined as time from date of randomization to date of first event of local invasive breast recurrence, regional invasive recurrence, or death due to any cause
To explore use of subsequent antineoplastic therapy	Incidence of subsequent antineoplastic therapy and time to first subsequent antineoplastic therapy
To explore healthcare resource utilization	Number of patients hospitalized, total number of hospitalizations, and length of stay in hospitals, number of patients with Emergency Room and additional visits

Source: [Study O12301C Primary Analysis CSR-Section 8].

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the design and protocol aspects of the NATALEE trial as stated above. Note that the NATALEE trial opened in December 2018, at which time iDFS using STEEP v1.0 criteria was the standard endpoint for most adjuvant breast cancer trials in the US. That endpoint includes second non-breast primary malignancy as one of the components of the definition. STEEP v2.0 recommended use of invasive breast cancer-free survival (IBCFS), which excludes second non-breast primary malignancy from the endpoint, over iDFS in most adjuvant trials, but these criteria were not published until May 2021. Given the concern for potentially increased risk of second primary malignancies related to nitrosamine impurities with ribociclib, the FDA review team considers the iDFS endpoint to be particularly relevant in NATALEE. As the number of second primary malignancies was ultimately very similar in the two treatment arms, inclusion of these events would be expected to increase the chance of a false negative outcome to the study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Efficacy analysis: All efficacy analyses were performed using the FAS which consisted of all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients were analyzed according to the treatment and strata they had been assigned to during the randomization procedure.

The primary efficacy variable of the study, iDFS, was defined as the time from the date of randomization to the date of the first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, death (any cause), contralateral invasive BC, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin). The primary efficacy analysis was the comparison of the distribution of iDFS between the two treatment arms. The null hypothesis stating that iDFS survival distributions of the two treatment arms are equivalent was tested against a one-sided alternative.

iDFS was analyzed using a Lan-DeMets (O'Brien-Fleming) alpha spending function and a non-binding Lan-DeMets (O'Brien-Fleming) beta spending function based on the data observed in the FAS up to the cut-off date, according to the treatment arm and strata assigned at

randomization. The survival distribution of iDFS was estimated using the Kaplan-Meier method. A stratified Cox regression was used to estimate the hazard ratio (HR) of iDFS along with 95% confidence interval (CI) using the same strata information as the primary efficacy comparison. As a sensitivity analysis to assess the impact of stratification, the two treatment arms were compared using the unstratified log-rank test. The HR together with the associated 95% confidence interval obtained using the unstratified Cox regression model was also presented. A multivariate stratified Cox regression model was fitted to evaluate the effect of other baseline demographic and disease characteristics on the estimated HR.

The distributions of the secondary efficacy endpoints RFS, DDFS and OS were estimated using the Kaplan-Meier method and compared between treatment groups using a stratified log-rank test at one-sided 2.5% level of significance. The HR for RFS, DDFS and OS were calculated, along with their 95% CI, using a stratified Cox model based on strata assigned at randomization.

Analysis of patient reported outcomes: As the main analysis and to best utilize the repeated PRO assessments, a repeated measures model for longitudinal data was used to estimate differences in PRO scores in all sub-scales obtained from EORTC QLQ-C30, the breast symptoms score of QLQ-BR23, the VAS of EQ-5D-5L and the anxiety domain and depression domain scores of HADS between treatment arms. The repeated measures model included terms for treatment, stratification factors assigned at randomization, time, baseline value as main effects, and an interaction term for treatment by time. All data collected until confirmation of first recurrence (including the assessment at confirmation of first recurrence) was included in the analysis.

Pharmacokinetic analysis: All PK analyses were based on the PAS, unless otherwise specified. Only evaluable PK concentrations which were not flagged for exclusion were used for summaries.

Safety analysis: All safety analyses were performed using the Safety set, which consisted of all randomized patients who received any study treatment (i.e., at least one dose of ribociclib or ET). Patients were analyzed according to the study treatment received. Separate AE summaries were presented by number and percentage of patients who had at least one AE, having at least one AE in each primary system organ class SOC and for each preferred term PT using MedDRA (version 25.1) coding. The safety summary tables within included treatment-emergent events/assessments with on-treatment AEs (new or worsened). Separate summaries for on-treatment deaths and all deaths (including post-treatment deaths), were produced by treatment arm, system organ class and preferred term. The primary cause of death was also displayed [Study O12301C Primary Analysis CSR-Section 2].

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the design and protocol aspects of the NATALEE trial as stated above. The statistical test for iDFS was based on ~5,000 patients randomized in a 1:1 ratio, where 500 iDFS events would provide a power of approximately 93% to detect a hazard ratio (HR) of 0.73, or approximately 85% to detect a HR of 0.76, with a 1-sided type 1 error of 0.025. There were three planned interim analyses

for iDFS (at 200, 350, and 425 iDFS events) in addition to the final analysis (at 500 iDFS events), using a Lan-DeMets (O'Brien-Fleming) alpha spending function. There was no type-1 error control for any secondary endpoint, including OS.

Protocol Amendments

The Applicant's Description:

The study protocol and the SAP were amended 3 times during the study. The key features of each protocol amendment are provided in the below table:

Amendment 1 (20-Jun-2019): Clinical safety was updated to include a statement that ribociclib is not recommended for use in combination with tamoxifen (due to increased risk of QT prolongation). Following consultation with EMA Scientific Advice Working Party and with the Steering Committee, the enrollment criteria were updated to include a subset of higher risk Stage II patients to reduce the heterogeneity of the study population. Also, identification of higher risk Stage II patients via gene expression tests was included. Study design rationale was updated to justify the open label study-design. Capping rule was amended to allow for a better representation of stage II and III patients. OS analysis at approximately two years after primary iDFS was added to OS analysis timelines. Statistical calculations were updated to reflect the increase in power for the iDFS endpoint (iDFS event rate was expected to increase as result of the change in population).

Amendment 2 (23-Jan-2020): Inclusion criteria was updated to reflect the postmenopausal definition as outlined in the breast cancer clinical guideline from the National Comprehensive Cancer Network (version 3.2019). Wording was added to provide clear guidance on ribociclib discontinuation when TEN is diagnosed, based on updates made to IB Ed.14. Urinalysis was removed from the Clinical Laboratory Collection Plan.

Amendment 3 (27-Aug-2020): Role of the CDK4/6 pathway in breast cancer was updated to describe emerging data from other CDK4/6 inhibitor studies. The study design rationale was updated to include an additional 1000 patients with Stage III eBC, with Stage II capped at 40% of total study population of approximately 5,000, based on emerging information external to the study. "Interim and final iDFS" and "Sample size calculation" sections updated because of the sample size increase. The required number of events for the final analysis of iDFS was updated to approximately 500 events to ensure the study power is retained at 85% for a hazard ratio of up to 0.76. An additional interim efficacy analysis at 85% information fraction) was added. Number of randomized patients required to observe the new targeted number of iDFS events was updated from 4,000 to 5,000 [Study O12301C Primary Analysis CSR-Section 9.8.1].

SAP amendments

The SAP was amended 3 times with key features outlined below:

- **Amendment 1** (26-Jul-2021) was mainly to implement changes due to Protocol amendment 3 (protocol v4.0) and to align with Novartis guidelines and program standards. The main

changes were the increase in sample size to 5000 patients, addition of an interim analysis at 85% IF, and updated futility boundary for IA 1.

- **Amendment 2** (15-Aug-2022): The key changes were clarifications of some analysis conventions such as central ECG assessments being a primary source of QT analysis , sensitivity analyses to assess the impact of COVID-19 deaths on iDFS and OS, gap analysis for iDFS and OS, subgroup definitions, updated time to event and duration of event endpoints, updated RDI/DI presentations, addition of a stratified multivariate Cox model, clarification of date derivations, and handling of censoring dates.

- **Amendment 3** (30-Aug-2023): The key changes were update for on-treatment window to align with the 3-year duration of ribociclib treatment, OS subgroup analysis added for stratification factors, and OS subgroup analysis added for stratification factors censoring COVID-19 deaths. Additional OS sensitivity analysis was performed to further evaluate the robustness of OS survival benefit. The OS analysis was repeated using the PPS, using the unstratified log-rank test and a multivariate stratified Cox regression model (fitted to evaluate the effect of other baseline demographic and disease characteristics on the estimated hazard ratio). The fitted model adjusted the treatment difference for key baseline and prognostic factors and included the following covariates: age (< 45 vs. 45-54 vs. 55-64 vs. ≥ 65), ER/PR status (ER+PR+ vs. other) and type of ET (letrozole vs. anastrozole).

  Based on its clinical relevance, the on-treatment death period was redefined taking the 36-month treatment period for ribociclib into account, i.e., deaths reported during and up to 30 days after the last dose of the treatment, up to a maximum of 36 months plus 30-days in either study arm.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the key elements of amendments to the protocol and SAP for the NATALEE trial.

8.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The study was conducted in full conformance with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in conformance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant in the study. The study protocol and 3 amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

The FDA's Assessment:

FDA generally agrees with the Applicant's statement of compliance with GCP in the NATALEE trial.

Financial Disclosure

The Applicant's Position:

Details are presented in Appendix 19.2.

The FDA's Assessment:

The financial disclosure information in Appendix 19.2 was reviewed. There were no financial conflicts identified that would be expected to compromise the integrity of NATALEE trial results.

Patient Disposition

Data:

Table 8: Patient disposition (final iDFS analysis, 21-Jul-2023 data cut-off) by treatment arm (FAS)

Disposition/Reason	ET + ribociclib N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Number of patients randomized	2549 (100)	2552 (100)	5101 (100)
Number of patients randomized but not treated	23 (0.9)	111 (4.3)	134 (2.6)
Number of patients treated with any treatment	2526 (99.1)	2441 (95.7)	4967 (97.4)
Number of patients who discontinued all treatment components	612 (24.0)	693 (27.2)	1305 (25.6)
Number of patients who discontinued ribociclib	1996 (78.3)	1 (< 0.1)	1997 (39.1)
Number of patients who discontinued NSAI	612 (24.0)	693 (27.2)	1305 (25.6)
Number of patients still on treatment	1914 (75.1)	1748 (68.5)	3662 (71.8)
Primary reason for ribociclib discontinuation			
Completed	1091 (42.8)	0	1091 (21.4)
Adverse event	498 (19.5)	0	498 (9.8)
Patient decision to discontinue treatment	135 (5.3)	0	135 (2.6)
Disease recurrence	122 (4.8)	0	122 (2.4)
Withdrawal by patient	82 (3.2)	0	82 (1.6)
Physician decision	24 (0.9)	0	24 (0.5)
Other	23 (0.9)	0	23 (0.5)
Lost to follow-up	8 (0.3)	0	8 (0.2)
Protocol deviation	6 (0.2)	1 (< 0.1)	7 (0.1)
Death	4 (0.2)	0	4 (0.1)
Endocrine therapy discontinuation	3 (0.1)	0	3 (0.1)
Primary reason for NSAI discontinuation			
Disease recurrence	168 (6.6)	224 (8.8)	392 (7.7)
Patient decision to discontinue treatment	138 (5.4)	126 (4.9)	264 (5.2)
Adverse event	131 (5.1)	113 (4.4)	244 (4.8)
Withdrawal by patient	117 (4.6)	162 (6.3)	279 (5.5)
Physician decision	28 (1.1)	32 (1.3)	60 (1.2)
Lost to follow-up	10 (0.4)	18 (0.7)	28 (0.5)

Disposition/Reason	ET + ribociclib N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Death	7 (0.3)	3 (0.1)	10 (0.2)
Other	7 (0.3)	9 (0.4)	16 (0.3)
Protocol deviation	6 (0.2)	6 (0.2)	12 (0.2)
Number of patients who have entered the follow-up phase	330 (12.9)	389 (15.2)	719 (14.1)
Number of patients who discontinued from trial	388 (15.2)	494 (19.4)	882 (17.3)
Withdrawal by patient	253 (9.9)	359 (14.1)	612 (12.0)
Death	84 (3.3)	88 (3.4)	172 (3.4)
Lost to follow-up	22 (0.9)	30 (1.2)	52 (1.0)
Physician decision	20 (0.8)	11 (0.4)	31 (0.6)
Other	4 (0.2)	2 (0.1)	6 (0.1)
Protocol deviation	4 (0.2)	4 (0.2)	8 (0.2)
Pregnancy	1 (< 0.1)	0	1 (< 0.1)

Source: [SCE Add. Study O12301C-Table 3-1]

The Applicant's Position:

Following completion of the screening phase, 5101 female and male patients were randomized in a 1:1 ratio to receive either ribociclib + NSAI (letrozole or anastrozole) + goserelin if applicable (henceforth referred to as the ribociclib + ET arm/group), or NSAI (letrozole or anastrozole) + goserelin if applicable (henceforth referred to as the ET only arm/group). There were 2549 patients randomized to the ribociclib + ET arm (99.1% of these patients were treated) and 2552 patients were randomized to the ET only arm (95.7% were of these patients were treated).

As of DCO (21-Jul-2023) for the FAS, study treatment remained ongoing in 1914 patients (75.1%) in the ribociclib + ET arm and 1748 patients (68.5%) in the ET only arm. In total, 1996 patients (78.3%) in the ribociclib + ET group had discontinued ribociclib, consisting of 1091 patients (42.8%) who completed the 3-year treatment duration and 905 patients (35.0%) who discontinued ribociclib before completing the 3-year treatment duration. The remaining 528 patients (20.7%) in the ribociclib + ET arm had yet to complete the 3-year treatment duration. Among these 528 patients, 108 (4.2%) were considered as treatment ongoing as of the DCO, but had completed their last ribociclib dispensation visit at 33 months prior to the end of ribociclib visit at 36 months. For those who discontinued ribociclib, the most frequent reason for ribociclib early discontinuation was AE (19.5%). The most frequent reason for NSAI discontinuation was disease recurrence (6.6% in the ribociclib + ET arm vs. 8.8% in the ET only arm) [Study O12301C EA&SU-Section 2.2].

The FDA's Assessment:

FDA generally concurs with the Applicant's position on patient disposition using the ITT population as stated above. Overall the rates of discontinuation of all treatment (24% on ribociclib + ET vs 27.2% on ET alone) and the rate of study discontinuation (15.2% vs 19.4%, respectively) were similar in the two treatment arms. The most common reason for ribociclib discontinuation was completion of treatment (42.8%). Discontinuations of ribociclib were more common than discontinuations of ET. Although this is expected in

part due to the design of the trial, which provides for 3 years of ribociclib and at least 5 years of ET, discontinuations due to AE were also much more common on the ribociclib + ET arm compared to the arm receiving ET alone (19.5% vs 5.1%).

In addition, see FDA analyses of the primary endpoint in Section 8.1.2 below.

Protocol Violations/Deviations

Data:

Table 9: Protocol deviations (FAS)

PD Term Deviation	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Number of patients with at least one protocol deviation	1868 (73.3)	1713 (67.1)	3581 (70.2)
IMP/NIMP	659 (25.9)	370 (14.5)	1029 (20.2)
Dosing & Administration	606 (23.8)	284 (11.1)	890 (17.4)
Supply	93 (3.6)	97 (3.8)	190 (3.7)
Wrong Treatment Administration	3 (0.1)	4 (0.2)	7 (0.1)
Informed Consent	477 (18.7)	480 (18.8)	957 (18.8)
Consenting Process	278 (10.9)	305 (12.0)	583 (11.4)
Timing of Consent	176 (6.9)	161 (6.3)	337 (6.6)
Failure to Obtain	54 (2.1)	38 (1.5)	92 (1.8)
Version	10 (0.4)	10 (0.4)	20 (0.4)
Other	9 (0.4)	14 (0.5)	23 (0.5)
Protocol Compliance	1591 (62.4)	1522 (59.6)	3113 (61.0)
Study Assessments & Procedures	1201 (47.1)	1259 (49.3)	2460 (48.2)
Inclusion / Exclusion	586 (23.0)	571 (22.4)	1157 (22.7)
Prohibitive Medication or Treatment	304 (11.9)	51 (2.0)	355 (7.0)
Other	26 (1.0)	11 (0.4)	37 (0.7)
Safety	39 (1.5)	33 (1.3)	72 (1.4)
Late / Unreported SAE / AESI / Pregnancy	39 (1.5)	33 (1.3)	72 (1.4)
Major/Critical Deviation Leading to Exclusion from Analysis Sets	29 (1.1)	18 (0.7)	47 (0.9)
Inclusion / Exclusion	29 (1.1)	17 (0.7)	46 (0.9)
Wrong Treatment Administration	0	1 (0.0)	1 (0.0)

A patient with multiple protocol deviations within the same PD term is counted only once for this PD term. Patients may have protocol deviations in more than one PD term.

Source: [Study O12301C Primary analysis CSR-Table 10-2]

The Applicant's Position:

Overall, 70.2% of patients reported at least one protocol deviation. The percentage of patients with deviations was slightly higher in the ribociclib + ET arm compared to that in the ET only arm (73.3% vs. 67.1%). A total of 47 patients (0.9%) were excluded from the PPS due to major deviations. Forty-six patients (0.9%) were excluded from the PPS due to inclusion/exclusion criteria not being met. In total, 2460 patients (48.2%) reported at least one study assessment and procedure PD and 1157 patients (22.7%) reported at least one inclusion/exclusion PD. The most commonly reported study assessment and procedure PD was mammography not regularly

assessed as per protocol (1062 patients, 20.8%). The most commonly reported inclusion/exclusion PD was baseline laboratory results criteria (blood salts i.e., potassium, calcium and magnesium) not met (218 patients, 4.3%) [Study O12301C Primary analysis CSR-Section 10.2].

The FDA's Assessment:

FDA reviewed the Applicant's position above. While the majority of protocol deviations was balanced between the two arms, the ribociclib + ET arm had higher protocol deviations due to "Dosing & Administration" and "Prohibitive Medication or Treatment." In response to an Information Request (IR), the Applicant provided additional information on the cause of the higher incidence of protocol deviations due to these two reasons, particularly on the ribociclib + ET arm.

Protocol deviations due to "Dosing & Administration": The primary cause was due to ribociclib "dose greater than the prescribed dose for >3 days or duration exceeded by 3 days or single dose ≥900 mg/day", in 245 patients. These patients received a mean of 2.7 extra days of ribociclib (median 2.0 days). The TEAEs experienced by these patients was compared with the TEAEs experienced overall by the patients who received ribociclib + ET, and generally comparable. No patient received a single dose ≥900 mg/day, and only one patient received ribociclib 600 mg for 147 days before this dose error was identified; the patient subsequently received ribociclib 400 mg. Section 2 Dosage & Administration of the ribociclib product labeling will clearly state that in the adjuvant treatment setting, the approved ribociclib dosage is 400 mg days orally for 21 days out of a 28 day cycle.

For the prohibited concomitant medications, the primary cause was due to short-term co-administration. One safety concern of prohibited concomitant medications for patients who received ribociclib + ET is QT prolongation. FDA's analysis of QT prolongation is provided in Section 8.2.4 below, and QT prolongation is already included in the ribociclib USPI as a Section 5 Warning and Precaution. The ribociclib USPI already clearly states prohibited concomitant medications.

Overall, the protocol deviations do not significantly impact the finding of a favorable benefit-risk assessment of ribociclib.

Table of Demographic Characteristics

Data:

Table 10: Demographic Characteristics

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Age group			
<45	611 (24.0)	591 (23.2)	1202 (23.6)
45 to 54	849 (33.3)	895 (35.1)	1744 (34.2)
55 to 64	682 (26.8)	700 (27.4)	1382 (27.1)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
≥ 65	407 (16.0)	366 (14.3)	773 (15.2)
Age (years)			
n	2549	2552	5101
Mean	52.9	52.7	52.8
SD	10.75	10.77	10.76
Min	24	24	24
Median	52.0	52.0	52.0
Max	90	89	90
Gender			
Male	11 (0.4)	9 (0.4)	20 (0.4)
Female	2538 (99.6)	2543 (99.6)	5081 (99.6)
Race			
White	1876 (73.6)	1868 (73.2)	3744 (73.4)
Black or African American	42 (1.6)	47 (1.8)	89 (1.7)
Asian	341 (13.4)	334 (13.1)	675 (13.2)
Native Hawaiian or Other Pacific Islander	3 (0.1)	1 (0.0)	4 (0.1)
American Indian or Alaska Native	4 (0.2)	3 (0.1)	7 (0.1)
Other	145 (5.7)	172 (6.7)	317 (6.2)
Missing	138 (5.4)	127 (5.0)	265 (5.2)
Ethnicity			
Hispanic or Latino	212 (8.3)	223 (8.7)	435 (8.5)
Not Hispanic or Latino	2076 (81.4)	2054 (80.5)	4130 (81.0)
Unknown	172 (6.7)	201 (7.9)	373 (7.3)
Missing	89 (3.5)	74 (2.9)	163 (3.2)
Region*			
Asia	281 (11.0)	290 (11.4)	571 (11.2)
Europe	1505 (59.0)	1506 (59.0)	3011 (59.0)
North America/Australia	624 (24.5)	612 (24.0)	1236 (24.2)
Latin America	139 (5.5)	144 (5.6)	283 (5.5)
ECOG performance status			
0	2106 (82.6)	2132 (83.5)	4238 (83.1)
1	440 (17.3)	418 (16.4)	858 (16.8)
Missing	3 (0.1)	2 (0.1)	5 (0.1)
Weight (kg)			
n	2534	2542	5076
Mean	72.4	72.2	72.3
SD	16.20	15.53	15.86
Min	38	41	38
Median	70.0	70.0	70.0
Max	166	169	169
Height (cm)			
n	2523	2522	5045
Mean	162.9	162.7	162.8
SD	6.78	6.85	6.81
Min	140	140	140
Median	163.0	163.0	163.0
Max	198	191	198
BMI (kg/m²)			

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
n	2518	2521	5039
Mean	27.3	27.3	27.3
SD	5.81	5.70	5.76
Min	16	15	15
Median	26.3	26.5	26.4
Max	56	59	59

Weight and height are the last non-missing assessments on or before the date of randomization.
BMI: body mass index is calculated based on raw data measurements.
*Asia includes China, Republic of Korea, and Taiwan. Europe includes Austria, Belgium, France, Germany, Hungary, Ireland, Italy, Poland, Romania, Russian Federation, Spain, and United Kingdom. North America/Australia includes Australia, Canada, and United States. Latin America includes Argentina and Brazil.

Source: [Study O12301C Primary analysis CSR-Table 10-7]

The Applicant's Position:

Demographic characteristics were well-balanced between the two treatment arms. Patients were representative of the population of pre- and postmenopausal women plus men with HR-positive, HER2-negative eBC.

The median age of patients in the study was 52 years (range: 24 to 90), with 34.2% of patients within the 45 to 54 years age group. Overall, 99.6% of patients were women and 0.4% of patients were men. The patients included were White (73.4%), Asian, (13.2%), Black or African American (1.7%), American Indian or Alaska Native (0.1%) and Pacific Islander (0.1%) The most frequent ethnicity was non-Hispanic or Latino (81.0%), followed by Hispanic or Latino (8.5%). Over half the patients (59.0%) in each treatment arm were based in Europe followed by North America/Australia (24.2%), Asia (11.2%) and Latin America (5.5%). The vast majority of patients (83.1%) had an ECOG performance status of zero at baseline [Study O12301C Primary analysis CSR-Section 10.4.1]

The FDA's Assessment:

FDA disagrees with the Applicant's characterization of the NATALEE trial as representative of the racial demographics of the U.S. population. More than half of the trial was enrolled in the European Union, and nearly three-quarters of the overall trial population was White.

In 2022, according to the Pew Research Center, there were approximately 48 million people in the United States who identified as Black, which is about 14% of the U.S. population. Black patients are markedly underrepresented (total n=89; 1.7%) in the NATALEE trial. According to American Cancer Society, among U.S. patients who develop breast cancer, Black patients were less likely to have HR+, HER2-negative subtype than white patients overall (57% vs 71%), but more likely to have regional disease (31% vs 24%) at diagnosis, with much higher mortality rates. The stage-matched five-year relative survival rates for patients with regional disease at diagnosis are 10% lower for Black

patients than for white patients. Black men are also more likely than men of other races to develop breast cancer both overall and considering the HR+, HER2-negative breast cancer subtype specifically. Black patients therefore have a very high degree of unmet medical need. Given that the NATALEE trial enrolled patients with high-risk Stage II or III HR+, HER2-negative disease, it should have been enriched for Black patients.

While this underrepresentation does not preclude approval of ribociclib in the adjuvant setting, it provides limited information with which to counsel Black patients on the risks and benefits of adding ribociclib to ET. More efforts to increase the diversity of the patients enrolled on cancer clinical trials to reflect the diversity of the U.S. patient population are urgently needed. A postmarketing commitment (PMC) will ask the Applicant to provide data from ongoing/planned clinical trials (e.g., adjuvant WIDER trial) or other sources to better characterize the efficacy and safety of ribociclib in racial minority subgroups, including the Black or African-American population. The rationale for and details of the PMC are discussed further in Section 13.

Other Baseline Characteristics

Data:

Table 11: Disease characteristics (FAS)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Tumor Location			
Right	1277 (50.1)	1258 (49.3)	2535 (49.7)
Left	1271 (49.9)	1287 (50.4)	2558 (50.1)
Bilateral	1 (0.0)	7 (0.3)	8 (0.2)
Missing	0	0	0
Histopathological grade at diagnosis - n (%)			
GX	30 (1.2)	32 (1.3)	62 (1.2)
G1	218 (8.6)	240 (9.4)	458 (9.0)
G2	1458 (57.2)	1451 (56.9)	2909 (57.0)
G3	521 (20.4)	549 (21.5)	1070 (21.0)
Not Done	292 (11.5)	258 (10.1)	550 (10.8)
Missing	30 (1.2)	22 (0.9)	52 (1.0)
T stage at diagnosis - n (%)			
TX	175 (6.9)	173 (6.8)	348 (6.8)
T0	4 (0.2)	7 (0.3)	11 (0.2)
Tis	2 (0.1)	3 (0.1)	5 (0.1)
T1	471 (18.5)	442 (17.3)	913 (17.9)
T2	1181 (46.3)	1235 (48.4)	2416 (47.4)
T3	471 (18.5)	472 (18.5)	943 (18.5)
T4	200 (7.8)	184 (7.2)	384 (7.5)
Missing	45 (1.8)	36 (1.4)	81 (1.6)
N stage at diagnosis - n (%)			
NX	272 (10.7)	264 (10.3)	536 (10.5)
N0	694 (27.2)	737 (28.9)	1431 (28.1)
N1	1050 (41.2)	1049 (41.1)	2099 (41.1)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
N2	332 (13.0)	292 (11.4)	624 (12.2)
N3	151 (5.9)	175 (6.9)	326 (6.4)
Missing	50 (2.0)	35 (1.4)	85 (1.7)
Ki67 score at initial diagnosis			
n	1861	1908	3769
Mean	27.1	27.1	27.1
SD	19.88	19.50	19.69
Min	0	0	0
Median	20.0	20.5	20.0
Max	99	100	100
Ki67 category at initial diagnosis			
≤ 14%	508 (19.9)	508 (19.9)	1016 (19.9)
> 14%	1353 (53.1)	1400 (54.9)	2753 (54.0)
≤ 20%	938 (36.8)	954 (37.4)	1892 (37.1)
>20%	923 (36.2)	954 (37.4)	1877 (36.8)
Missing	688 (27.0)	644 (25.2)	1332 (26.1)
Histopathological grade on surgical specimen - n (%)			
GX	32 (1.3)	30 (1.2)	62 (1.2)
G1	213 (8.4)	217 (8.5)	430 (8.4)
G2	1460 (57.3)	1432 (56.1)	2892 (56.7)
G3	684 (26.8)	702 (27.5)	1386 (27.2)
Not Done	159 (6.2)	168 (6.6)	327 (6.4)
Missing	1 (0.0)	3 (0.1)	4 (0.1)
T stage on surgical specimen - n (%)			
TX	20 (0.8)	9 (0.4)	29 (0.6)
T0	56 (2.2)	52 (2.0)	108 (2.1)
Tis	16 (0.6)	19 (0.7)	35 (0.7)
T1	774 (30.4)	761 (29.8)	1535 (30.1)
T2	1162 (45.6)	1198 (46.9)	2360 (46.3)
T3	427 (16.8)	422 (16.5)	849 (16.6)
T4	92 (3.6)	91 (3.6)	183 (3.6)
Missing	2 (0.1)	0	2 (0.0)
N stage on surgical specimen - n (%)			
NX	2 (0.1)	5 (0.2)	7 (0.1)
N0	378 (14.8)	418 (16.4)	796 (15.6)
N1	1062 (41.7)	1039 (40.7)	2101 (41.2)
N2	733 (28.8)	690 (27.0)	1423 (27.9)
N3	372 (14.6)	399 (15.6)	771 (15.1)
Missing	2 (0.1)	1 (0.0)	3 (0.1)
Ki67 score on surgical specimen [1]			
n	1269	1332	2601
Mean	20.6	20.9	20.7
SD	17.82	18.15	17.99
Min	0	0	0
Median	15.0	15.0	15.0
Max	99	98	99
Ki67 category on surgical specimen			

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
≤ 14%	541 (21.2)	577 (22.6)	1118 (21.9)
> 14%	728 (28.6)	755 (29.6)	1483 (29.1)
≤ 20%	817 (32.1)	864 (33.9)	1681 (33.0)
> 20%	452 (17.7)	468 (18.3)	920 (18.0)
Missing	1280 (50.2)	1220 (47.8)	2500 (49.0)
Time since initial diagnosis (months)			
n	2517	2528	5045
Mean	11.8	11.8	11.8
SD	3.53	3.58	3.55
Min	1	1	1
Median	11.7	11.7	11.7
Max	23	27	27
Predominant histology - n (%)			
Invasive ductal carcinoma NOS	1857 (72.9)	1881 (73.7)	3738 (73.3)
Invasive lobular	455 (17.9)	450 (17.6)	905 (17.7)
Carcinoma medullary	1 (0.0)	1 (0.0)	2 (0.0)
Mucinous	17 (0.7)	16 (0.6)	33 (0.6)
Papillary	18 (0.7)	12 (0.5)	30 (0.6)
Tubular	5 (0.2)	3 (0.1)	8 (0.2)
Ductal Carcinoma In Situ	1 (0.0)	0	1 (0.0)
Lobular Carcinoma In Situ	0	0	0
Other	194 (7.6)	189 (7.4)	383 (7.5)
Missing	1 (0.0)	0	1 (0.0)
Prior surgery - n (%)			
Mastectomy	1664 (65.3)	1691 (66.3)	3355 (65.8)
Breast conserving surgery	978 (38.4)	963 (37.7)	1941 (38.1)
Axillary lymph node dissection	2165 (84.9)	2149 (84.2)	4314 (84.6)
Sentinel lymph node biopsy	926 (36.3)	920 (36.1)	1846 (36.2)
Other	143 (5.6)	162 (6.3)	305 (6.0)
Missing	0	0	0
HER2 ISH result prior to surgery (reported only if performed) - n (%)			
Amplification	4 (0.2)	7 (0.3)	11 (0.2)
Non-Amplification	612 (24.0)	653 (25.6)	1265 (24.8)
Equivocal	19 (0.7)	13 (0.5)	32 (0.6)
Unknown	6 (0.2)	11 (0.4)	17 (0.3)
HER2 ISH result from the surgical specimen (reported only if performed) - n (%)			
Amplification	2 (0.1)	1 (0.0)	3 (0.1)
Non-Amplification	417 (16.4)	423 (16.6)	840 (16.5)
Equivocal	1 (0.0)	1 (0.0)	2 (0.0)
Unknown	2 (0.1)	2 (0.1)	4 (0.1)
HER2 IHC score prior to surgery (reported only if performed) - n (%)			
0	856 (33.6)	881 (34.5)	1737 (34.1)
1+	862 (33.8)	813 (31.9)	1675 (32.8)
2+	464 (18.2)	480 (18.8)	944 (18.5)
3+	5 (0.2)	5 (0.2)	10 (0.2)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Unknown	21 (0.8)	21 (0.8)	42 (0.8)
HER2 IHC score from the surgical specimen (reported only if performed) - n (%)			
0	625 (24.5)	610 (23.9)	1235 (24.2)
1+	513 (20.1)	516 (20.2)	1029 (20.2)
2+	235 (9.2)	262 (10.3)	497 (9.7)
3+	1 (0.0)	3 (0.1)	4 (0.1)
Unknown	6 (0.2)	10 (0.4)	16 (0.3)
ER/PR combination statuses - n (%)			
ER+/PR+	2172 (85.2)	2132 (83.5)	4304 (84.4)
ER+/PR-	359 (14.1)	392 (15.4)	751 (14.7)
ER-/PR+	3 (0.1)	12 (0.5)	15 (0.3)
ER+/UNK	10 (0.4)	13 (0.5)	23 (0.5)
UNK/PR+	2 (0.1)	2 (0.1)	4 (0.1)
UNK/PR-	1 (0.0)	1 (0.0)	2 (0.0)
UNK/UNK	2 (0.1)	0	2 (0.0)
AJCC 8th ed. anatomic stage - n (%)			
Stage 0	0	0	0
Stage I	9 (0.4)	5 (0.2)	14 (0.3)
Stage II	1011 (39.7)	1034 (40.5)	2045 (40.1)
Stage III	1528 (59.9)	1512 (59.2)	3040 (59.6)
Stage IV	0	0	0
Missing	1 (0.0)	1 (0.0)	2 (0.0)
Genomic test			
Endopredict	23 (0.9)	28 (1.1)	51 (1.0)
Mammaprint	46 (1.8)	51 (2.0)	97 (1.9)
Oncotype DX	120 (4.7)	129 (5.1)	249 (4.9)
Pam50	38 (1.5)	29 (1.1)	67 (1.3)
Other	109 (4.3)	103 (4.0)	212 (4.2)
N status for subgroup analysis used in AJCC Stage derivation [2]			
N0	285 (11.2)	328 (12.9)	613 (12.0)
N1-N3	2261 (88.7)	2219 (87.0)	4480 (87.8)
>N3	0	0	0
Missing	3 (0.1)	5 (0.2)	8 (0.2)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Subjects may have had more than one prior surgery but are only counted once per category.			
T stage category T1 collects T1mi, T1a, T1b, and T1c. Category T4 collects T4a, T4b, T4c, and T4d.			
N stage category N0 collects N0 and N0(i+). Category N1 collects N1, N1a, N1c, and N1mi. Category N2 collects N2a, N2b, and N2c. Category N3 collects N3a, N3b, and N3c.			
AJCC 8th ed. category Stage 1 collects Stage IA and Stage IB. Category Stage II collects Stage IIIA and Stage IIB. Category Stage III collects Stage IIIA, Stage IIIB, and Stage IIIC. Stage is derived using TNM from surgery for patients having not received neo-/adjuvant treatment, or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received neo-/adjuvant treatment.			
Patients may have had more than one Genomic test type but are only counted once per type.			
[1] Ki67 per surgical specimen (if available, otherwise at diagnosis) was used for subgroup iDFS analysis.			
[2] Included in missing category are patients having Nx. These patients are either unable to be staged or have been staged with Nx and T4(x) as Stage IIIB.			

Source: [Study O12301C Primary analysis CSR-Table 10-8]

The Applicant's Position:

Treatment arms were generally well balanced and represented the intended eBC patient population with respect to baseline characteristics (including Anatomic Stage Group and nodal status). The proportion of patients with Anatomic Stage Group II disease was well balanced between both treatment arms (39.7% of patients in the ribociclib + ET arm vs. 40.5% of patients in the ET only arm). Similarly for Anatomic Stage Group III disease, a balance between both treatment arms was observed (59.9% of patients in the ribociclib + ET arm vs. 59.2% of patients in the ET only arm). A total of 285 patients (11.2%) in the ribociclib + ET arm and 328 patients (12.9%) in the ET only arm were N0 based on nodal status used in AJCC Stage derivation. The predominant histology was invasive ductal carcinoma (reported in 72.9% of patients in the ribociclib + ET arm and 73.7% of patients in the ET only arm. Although not required for all patients (and performed locally), the total number of patients enrolled with Ki67 scores ≤ 20% and > 20% were comparable (37.1% vs. 36.8%). All patients were HER2-negative (by protocol definition) with the exception of 8 patients (0.3%) in the ribociclib + ET arm and 10 patients (0.4%) in the ET only arm who were excluded from the Per Protocol Set [Study O12301C Primary analysis CSR-Section 10.4.2].

The FDA's Assessment:

FDA agrees that the disease characteristics at baseline are generally well-balanced between the two treatment arms and are reflective of the population for which the Applicant is seeking an indication in early breast cancer. As discussed elsewhere in the review, the patients in the NATALEE trial were much higher risk than the overall population with HR+, HER2-negative breast cancer in the US, based upon the grade, stage, and extent of nodal involvement, and therefore these results should not be extrapolated to a lower-risk population of patients.

The proposed indication in patients with stage II and III HR+, HER2-negative breast cancer accurately reflects the study population; however, there is more limited information

on the benefit of ribociclib in patients with node-negative breast cancer as only 613 (12%) patients on NATALEE had N0 disease based upon nodal status used in AJCC staging, including 285 (11.2%) of patients on the ribociclib + ET arm. In subgroup analyses by nodal status, the iDFS favored ribociclib + ET over ET alone regardless of nodal status; the hazard ratio point estimates were similar for patients with N0 disease [HR 0.72 (95% CI: 0.41, 1.27)] and with N1-N3 disease [HR 0.76 (95% CI: 0.63, 0.91)], albeit with wider confidence intervals that cross 1, given the smaller sample size in the N0 subgroup. See FDA's analysis of iDFS by Stage and nodal status in Section 8.1.2 and Table 20.

Stratification

Data:

Table 12: Randomization by stratification factor (Full analysis set)

	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	All patients N=5101 n (%)
Stratification factor at randomization			
Menopausal Status			
Premenopausal women and men	1125 (44.1%)	1128 (44.2%)	2253 (44.2%)
Postmenopausal women	1424 (55.9%)	1424 (55.8%)	2848 (55.8%)
AJCC Stage			
Anatomic Stage Group II	1076 (42.2%)	1078 (42.2%)	2154 (42.2%)
Anatomic Stage Group III	1473 (57.8%)	1474 (57.8%)	2947 (57.8%)
Prior Chemotherapy			
Yes	2214 (86.9%)	2218 (86.9%)	4432 (86.9%)
No	335 (13.1%)	334 (13.1%)	669 (13.1%)
Geographic Region			
NA/WE/O	1563 (61.3%)	1565 (61.3%)	3128 (61.3%)
ROW	986 (38.7%)	987 (38.7%)	1973 (38.7%)

Strata as entered in the IRT during randomization
NA/WE/O: North America/Western Europe/Oceania; ROW: Rest of World

Source: Study O12301C Primary analysis CSR-Table 10-5

The Applicant's Position:

Stratification according to menopausal status (premenopausal women, and men vs. postmenopausal women), AJCC 8th edition Stage (Stage II vs. Stage III), prior neoadjuvant/adjuvant chemotherapy (yes vs. no), and geographical region (North America/Western Europe/Oceania vs. rest of the world) was incorporated in the randomization design. The number of patients randomized according to each stratification factor (by IRT) was comparable between the ribociclib + ET arm and ET only arms [Study O12301C Primary analysis CSR-Section 10.3.1].

The FDA's Assessment:

FDA agrees that stratification factors are generally well-balanced between the two treatment arms. In addition, the concordance rates were high between IRT and CRF, with 98% concordance in menopausal status, 95% concordance in AJCC 8th edition staging, 98% concordance in prior neoadjuvant/adjuvant chemotherapy, and 100% concordance in geographical region.

Of note, consistent with the baseline characteristics noted above, including a high rate of node positivity and grade 2 or 3 tumors, 87% of participants received (neo)adjuvant chemotherapy, which reflects the high-risk nature of the NATALEE population. The benefit-risk assessment should not be extrapolated to a lower-risk U.S. population of patients with HR+, HER-2 negative early breast cancer.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance: No formal treatment compliance measurements for ribociclib, letrozole, anastrozole and goserelin were performed. Compliance was assessed by the Investigator examining the records of drug administration and the numbers of boxes as well as the tablets/capsules dispensed, received, and returned. The records of administration for ribociclib, NSAI (letrozole or anastrozole), and goserelin are provided [Study O12301C Primary analysis CSR-Section 10.6.3].

Concomitant therapy: Overall, a similar proportion of patients received concomitant medications during the study in the ribociclib + ET arm and in the ET only arm (92.3% vs. 85.9%). No imbalance was evident in the frequency or type of medication used.

Concomitant use of bisphosphonates was similar between treatment arms (15.1% of patients in the ribociclib + ET arm and 15.2% of patients in the ET only arm). Concomitant use of denosumab, primarily for the treatment of osteoporosis and to increase bone mass due to high risk of fracture in the adjuvant setting, was also reasonably well balanced between treatment arms (2.35% of patients in the ribociclib + ET arm and 2.94% of patients in the ET only arm). The use of concomitant systemic corticosteroids was low and comparable in both treatment arms (0.4% of patients in ribociclib + ET arm and 0.5% of patients in the ET only arm). Systemic corticosteroid combinations were concomitantly used by 0.3% of patients in the ribociclib + ET arm and 0.1% of patients in the ET only arm.

Overall, 17.8% of patients in the ribociclib + ET arm and 18.4% of patients in the ET only arm received at least one concomitant medication that was prohibited by this study. The most commonly (≥ 2.5%) used prohibited medications in the ribociclib + ET arm compared to the ET only arm were ondansetron (3.7% vs. 2.5%), azithromycin (3.1% vs. 2.5%) and ciprofloxacin (2.5% vs. 2.4%) [Study O12301C Primary analysis CSR-Section 10.5.2].

Rescue medication

Not applicable as no rescue medications were allowed in the study.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the data. The number of patients who received a concomitant medication prohibited by the study (approximately 18% in each arm) is high and of concern given that many of these drug-drug interactions, including the three most common prohibited concomitant medications used in the study, can increase the risk of QT prolongation and Torsades de Pointes. The use of prohibited concomitant medications was distributed equally across study arms. This likely reflects what will inadvertently occur in more typical use in the postmarket setting with three years of ribociclib in a curative intent population. It is therefore reassuring that even with 1 in 5 patients on study having received a prohibited medication, both QT prolongation of >60 ms from baseline or to >480 ms in patients on ribociclib + ET, as well as AESIs that may reflect undetected QT prolongation, were uncommon, likely due to the lower dose of 400 mg used in the adjuvant setting. See additional safety information regarding this issue in Section 8.2.

Efficacy Results

Efficacy claims for use of ribociclib 400 mg in combination with ET (AI: anastrozole or letrozole) and goserelin, if applicable, as adjuvant therapy for HR-positive, HER2-negative eBC are based on results from the final iDFS analysis (data cut-off date: 21-Jul-2023) and primary iDFS analysis at IA3 (data cut-off date: 11-Jan-2023) from the Phase III Study O12301C [CO Study O12301C-Section 4].

- The prespecified primary iDFS analysis IA3 was performed at 426 iDFS events, after which the DMC concluded that the iDFS results met the criteria to demonstrate statistically significant efficacy. As of the DCO date for IA3, the median duration of study follow-up from randomization to DCO was 34.0 months. The median follow-up for iDFS was 27.7 months.
- The results of the final iDFS analysis (509 iDFS events) are reported in this document. The median duration of study follow-up for this DCO was 40.3 months (from randomization to DCO), with a minimum duration of follow-up of 27 months. The median follow-up for iDFS is 33.3 months for both arms.

The totality of the data for the primary iDFS analysis (IA3) is provided in [Study O12301C Primary analysis CSR]. The updated data from the final iDFS analysis is provided in [Study O12301C EA&SU].

Primary Endpoint - Magnitude of treatment effect and robustness of iDFS analysis

Data:

Table 13: Log-rank test results for iDFS (FAS)

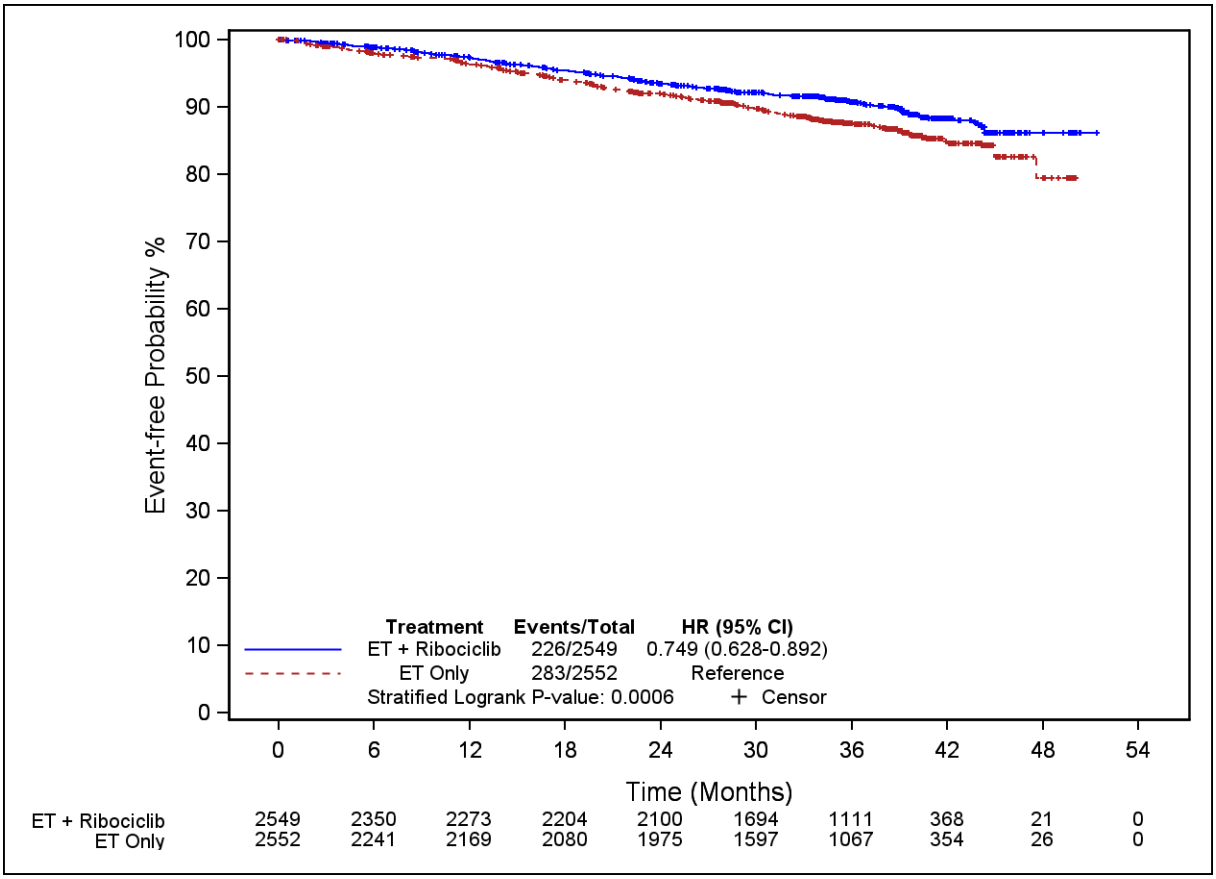
Treatment	n/N (%)	Comparison	Z-statistic	p-value*
Primary iDFS Analysis (DCO 11-Jan-2023)				
Ribociclib + ET	189/2549 (7.4)	vs. ET Only	-2.9847	0.0014

Treatment	n/N (%)	Comparison	Z-statistic	p-value*
ET Only	237/2552 (9.3)			
Final iDFS Analysis (DCO 21-Jul-2023)				
Ribociclib + ET	226/2549 (8.9)	vs. ET Only	-3.2528	0.0006
ET Only	283/2552 (11.1)			

n is the number of iDFS events.
N = total number of patients included in the analysis.
* 1-sided p-value for log-rank test stratified by premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.

Source: [CO Study O12301C-Table 4-2]

Figure 2: Kaplan-Meier plot for iDFS (FAS) - final iDFS analysis (21-Jul-2023 data cut-off)



Source: [SCE Study O12301C-Figure 3-1]

The Applicant's Position:

The ribociclib + ET arm demonstrated statistically significant and clinically superior efficacy over the ET only arm for the primary endpoint of iDFS per Investigator assessment [Study O12301C Primary analysis CSR], which was maintained over time. At the final iDFS analysis,

there was an estimated 25.1% relative reduction in the risk of an iDFS event (HR 0.749; 95% CI: 0.628, 0.892; one-sided stratified log-rank test nominal p-value = 0.0006) [SCE Study O12301C-Tables 3-10 and 3-11], [SCE Add. Study O12301C-Tables 3-2 and 3-3].

At the final iDFS analysis, the Kaplan-Meier iDFS curves diverged from approximately 3 months after start of treatment, corresponding to time of first STEEP clinical evaluation. In general, the iDFS event-free probability remained higher in the ribociclib + ET arm, indicating an early, sustained benefit with the ribociclib combination, which was maintained over time (Figure 2). As of the data cut-off date for the final iDFS analysis, there were approximately 5.6 months of additional follow-up for iDFS, with median duration of iDFS follow-up (from randomization to last recurrence assessment) of 33.3 months for both arms.

The 3-year iDFS rates for the final iDFS analysis were 90.7% (95% CI: 89.3, 91.8) in the ribociclib + ET arm and 87.6% (95% CI: 86.1, 88.9) in the ET only arm, reflecting a 3.1% absolute benefit favoring ribociclib + ET.

There were fewer iDFS events (8.9% vs. 11.1%) reported in the ribociclib + ET arm compared to the ET only arm. This trend is consistent with the primary iDFS analysis results (4.7% vs. 6.7%, distant recurrence events).

Robustness and consistency of iDFS analysis

Results of the iDFS analysis based on the PPS were consistent with the final iDFS analysis based on the FAS (one-sided stratified log-rank test p-value=0.0005; stratified Cox regression model HR=0.746; 95% CI: 0.626, 0.890). In addition, multiple sensitivity analyses based on excluding missing iDFS assessment, backdating iDFS, new anticancer therapy, clinical recurrence, and death due to COVID-19, were supportive of the final iDFS analysis results.

Consistent treatment effect-iDFS subgroup analyses

Consistency of iDFS benefit was evident across stratification factors of anatomic stage, prior (neo)adjuvant chemotherapy, menopausal status, and geographic region, and other subgroups. The ITT results of IDFS did not appear to be driven by any particular subgroup [CO Study O12301-Section 4.3.1.1].

The FDA's Assessment:

FDA agrees that the ribociclib + ET arm demonstrated a statistically significant improvement compared to the ET only arm for the primary endpoint of iDFS per investigator assessment at IA3. However, at IA3, there was a large amount of censoring for iDFS as only 20% of patients had completed 3-years of adjuvant ribociclib. Due to the FDA's concern for a possible diminishing iDFS effect with longer follow-up, FDA requested that the Applicant continue NATALEE until the final iDFS analysis.

At the final iDFS analysis (DCO: July 21, 2023), 43% of patients had completed 3 years of adjuvant ribociclib. There were 226 iDFS events in 2549 patients in the ribociclib + ET arm compared to 283 iDFS events in 2552 patient in the ET only arm at the final iDFS analysis. The final iDFS HR was 0.75 (95% CI: 0.63, 0.89), which was consistent with iDFS results at

IA3. The reasons for iDFS censoring at the time of final iDFS analysis are summarized in Table 14 below.

Table 14: FDA – iDFS Censoring Reasons (final iDFS analysis)

	Ribociclib + ET N=2549 (%)	ET only N=2552 (%)
Number of patients with iDFS event	226 (8.9)	283 (11.1)
Number of patients censored	2323 (91.1)	2269 (88.9)
Reason for censoring		
Ongoing without event	2073 (81.3)	1901 (74.5)
Withdrew consent	233 (9.1)	343 (13.4)
Lost to follow-up	17 (0.7)	25 (1.0)

Source: FDA Analysis

Of note, FDA was concerned that there appeared to be an imbalance in the number of patients censored due to withdrawal of consent. FDA further examined the timing of censoring for patients who were censored for withdrawal of consent, as shown in Table 15.

Table 15: FDA – Timing of Censoring for Patients Censored for Withdrawal of Consent

Time Censored	Ribociclib + ET N=2549 (%)	ET Only N=2552 (%)
Randomization	84 (3.3)	201 (7.9)
>0-6 Months	66 (2.6)	43 (1.7)
6-12 Months	30 (1.2)	21 (0.8)
12-24 Months	31 (1.2)	47 (1.8)
24-48 Months	22 (0.9)	31 (1.2)
Total	233 (9.1)	343 (13.4)

Source: FDA Analysis

From this, it appeared that the imbalance was largely due to patients who were censored at randomization for withdrawal of consent.

Therefore, FDA conducted several sensitivity analyses to assess the impact of the imbalance in patients who were censored at randomization due to withdrawal of consent. The sensitivity analyses considered various approaches to impute iDFS data for these patients, and results are summarized in Table 16.

Table 16: FDA – iDFS Sensitivity Analyses to Account for Imbalance in Patients Censored at Randomization for Withdrawal of Consent

Sensitivity Analysis Description	HR (95% CI)
For patients censored at randomization for withdrawal of consent:	
1. Impute iDFS for patients in both arms from the best 20% for iDFS in both arms	0.80 (0.67, 0.95)
2. Impute iDFS for patients in both arms from the best 20% for iDFS in ET Only arm only	0.82 (0.69, 0.98)
3. Impute iDFS for patients in the ET Only arm from the best 20% for iDFS in both arms	0.81 (0.68, 0.97)
4. Impute iDFS for patients in the ET Only arm from the best 20% for iDFS in the ET Only arm only	0.82 (0.69, 0.97)

Source: FDA Analysis

Results of the sensitivity analyses were generally consistent with results of the final iDFS analysis (iDFS HR of 0.75 [95% CI: 0.63, 0.89]), even when considering the most conservative scenario in which only patients on the ET only arm had iDFS times imputed from the best 20% for iDFS in both arms. FDA also examined the baseline characteristics for the patients who were censored at baseline for withdrawal of consent and did not identify any major difference in prognosis for this group of patients. Thus, it does not appear that this imbalance impacted results in a way that would change the overall benefit-risk assessment.

In addition, FDA agrees that the iDFS results at the final analysis were consistent across multiple sensitivity analyses, including those excluding missing assessments and those considering different censoring rules. Results of iDFS in exploratory subgroups of interest are shown in the next section and were generally consistent with the primary analysis.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 17: Secondary efficacy results (Study O12301C) - final iDFS analysis (21-Jul-2023 data cut-off)

	Overall study population
N	FAS = 5101: 2549 patients in ribociclib + ET arm, and 2552 patients in ET only arm
RFS	7.5% vs. 9.7% in favor of ribociclib + ET (one sided stratified log-rank test p-value=0.0004) Cox regression model: estimated 27.3% reduction in the risk of RFS in the ribociclib + ET arm; hazard ratio=0.727 (95% CI: 0.602, 0.877) Kaplan-Meier method: 3-year RFS rates of 92.1% (95% CI: 90.9, 93.2) in the ribociclib + ET arm and 89.1% (95% CI: 87.6, 90.4) in the ET only arm, translating to a 3.0% improvement in the 3-year rate of RFS in favor of ribociclib + ET

	Overall study population
DDFS	8.0% vs. 10% in favor of ribociclib + ET (one sided stratified log-rank test p-value=0.0010) Cox regression model: estimated 25.1% reduction in the risk of DDFS in the ribociclib + ET arm; hazard ratio=0.749 (95% CI: 0.623-0.900) Kaplan-Meier method: 3-year DDFS rates of 91.5% (95% CI: 90.2, 92.7) in the ribociclib + ET arm and 88.9% (95% CI: 87.4, 90.2) in the ET only arm, translating to a 2.6% improvement in the 3-year rate of DDFS in favor of ribociclib + ET
OS	No detriment observed for patients in the ribociclib + ET arm Log-rank analysis: 84 (3.3%) deaths in the ribociclib + ET arm, and 88 (3.4%) in the ET only arm: (one-sided stratified log-rank test nominal p-value = 0.2263) Cox regression model: estimated 10.8% reduction in the risk of death in the ribociclib + ET arm; hazard ratio=0.892 (95% CI: 0.661, 1.203) Kaplan-Meier method: 3-year OS rates were 97.0% (95% CI: 96.2, 97.6) in the ribociclib + ET arm and 96.1% (95% CI: 95.1, 96.9) in the ET only arm *Sensitivity analyses for OS (including based on PPS, per CRF, unstratified log-rank test and Cox model, stratified Cox model adjusting for baseline covariates, and censoring for patients with death due to COVID) provide further support that there is a positive trend in favor of the ribociclib + ET arm, with HRs ranging from 0.837 to 0.910
*Exploratory	

Source: [CO Study O12301C-Section 4.3.2]

The Applicant's Position:

Secondary efficacy endpoints

Results for the secondary efficacy endpoints support the clinical benefit of ribociclib in combination with ET as adjuvant therapy, with no detriment in OS.

Ribociclib + ET was associated with significant improvements in RFS and DDFS, with HRs of 0.72 (95% CI: 0.584, 0.884) and 0.74 (95% CI: 0.603-0.905) for the primary analysis/IA3, and HRs of 0.73 (95% CI: 0.602, 0.877) and 0.75 (95% CI: 0.623-0.900) for the final iDFS analysis, respectively. While OS results were immature, OS data at this final iDFS analysis showed no detriment in OS with the addition of ribociclib to ET. A numerically lower mortality rate in the ribociclib + ET arm has been reported, with a total of 84 (3.3%) events in the ribociclib + ET arm, and 88 (3.4%) in the ET only arm. Of note, in this analysis, the OS event rate is lower than anticipated (172 deaths observed vs. 271 deaths anticipated in the protocol at the final iDFS analysis) [CO Study O12301C- Section 4.3.2].

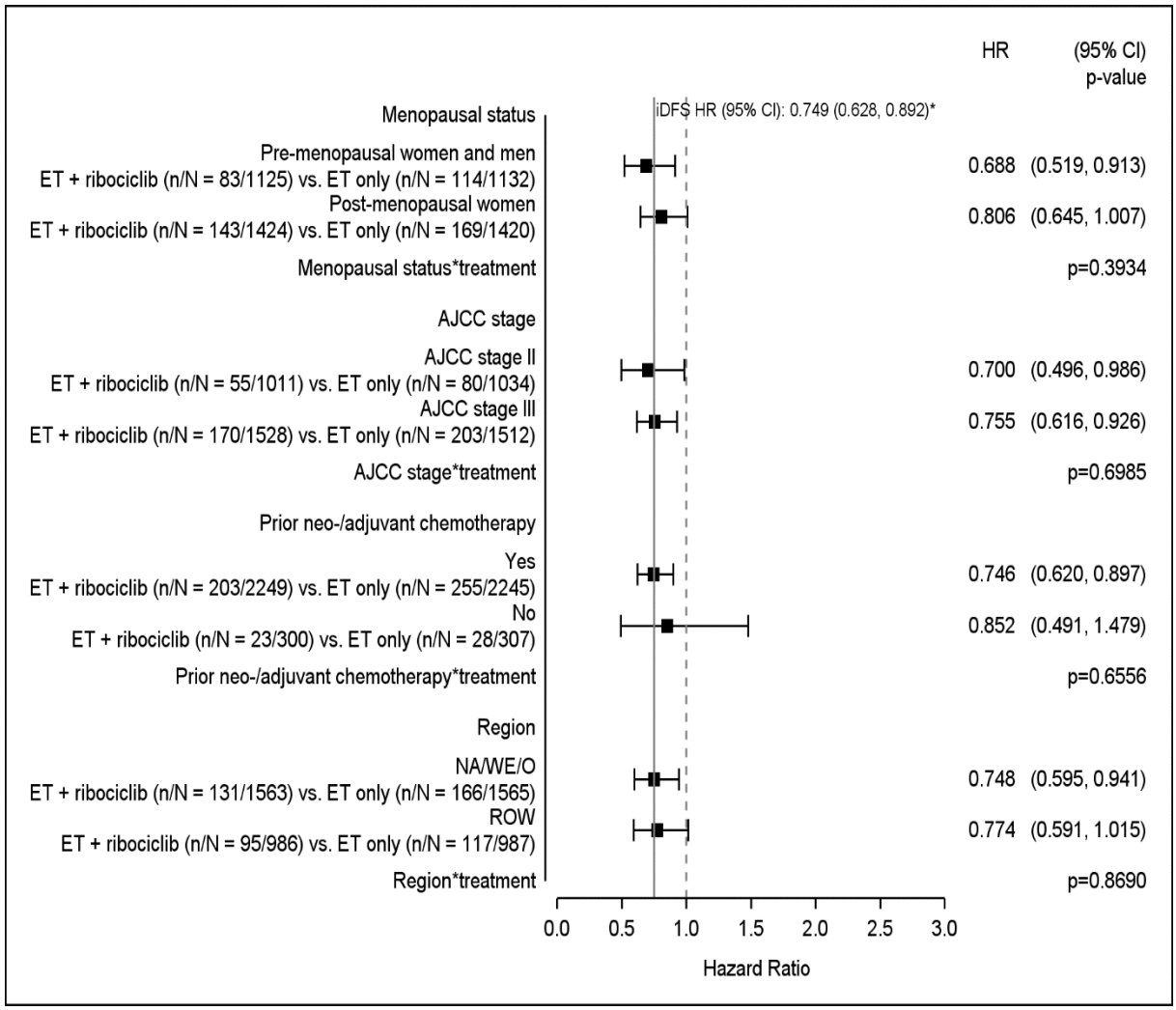
DRFS (exploratory efficacy analysis)

For the final iDFS analysis, there was an estimated 26.2% relative reduction in the risk of DRFS for patients in the ribociclib + ET arm (hazard ratio = 0.738; 95% CI: 0.606, 0.898). The DRFS distribution was estimated using the Kaplan-Meier method. There were 178 events in the ribociclib + ET arm vs. 227 events in the ET only arm; one-sided nominal p-value = 0.0012 [CO Study O12301C-Section 4.3.2.1].

Efficacy in subpopulations

Data:

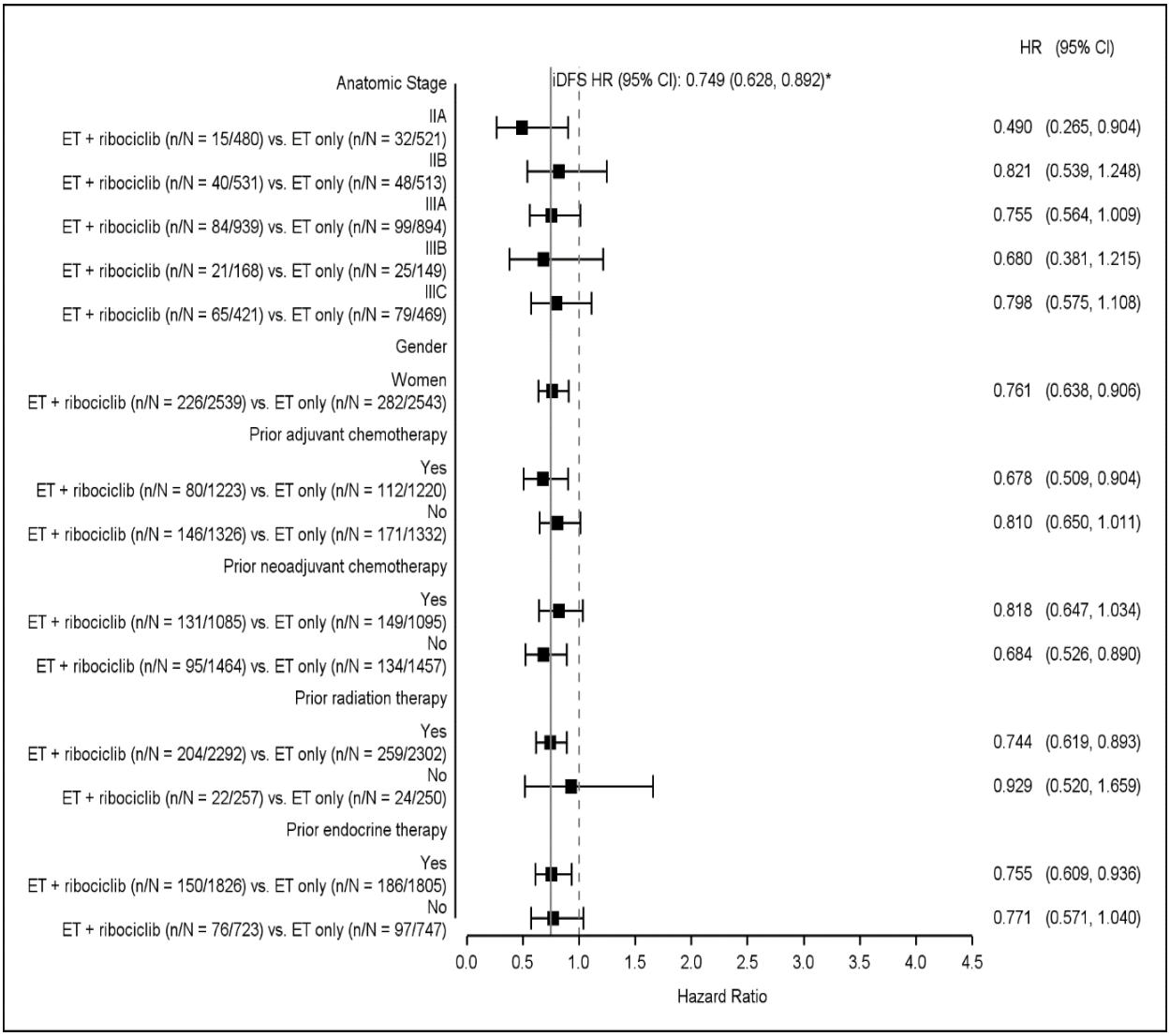
Figure 3: Forest plot of iDFS by stratum (final iDFS analysis, 21-Jul-2023 data cut-off (FAS)

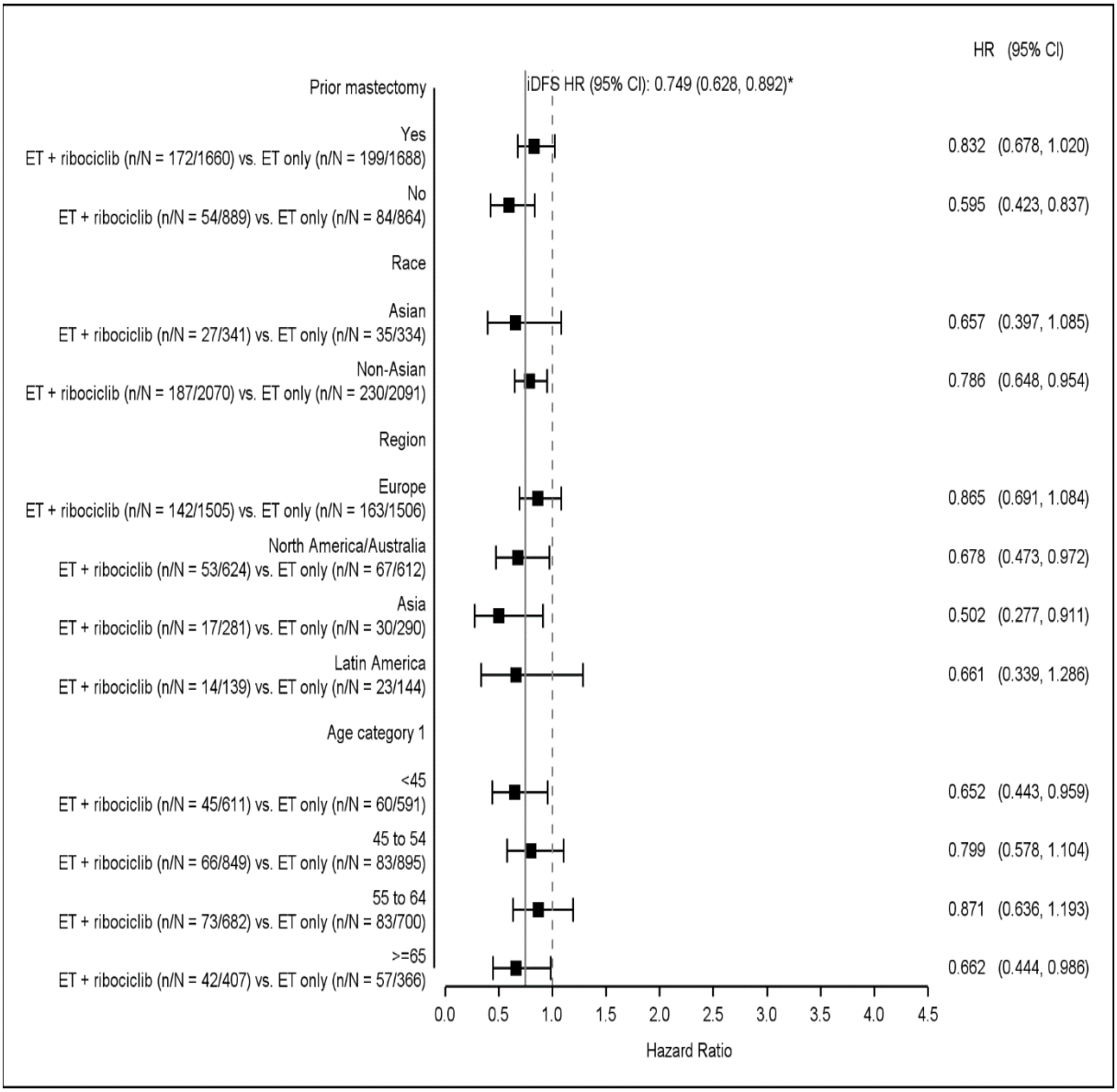


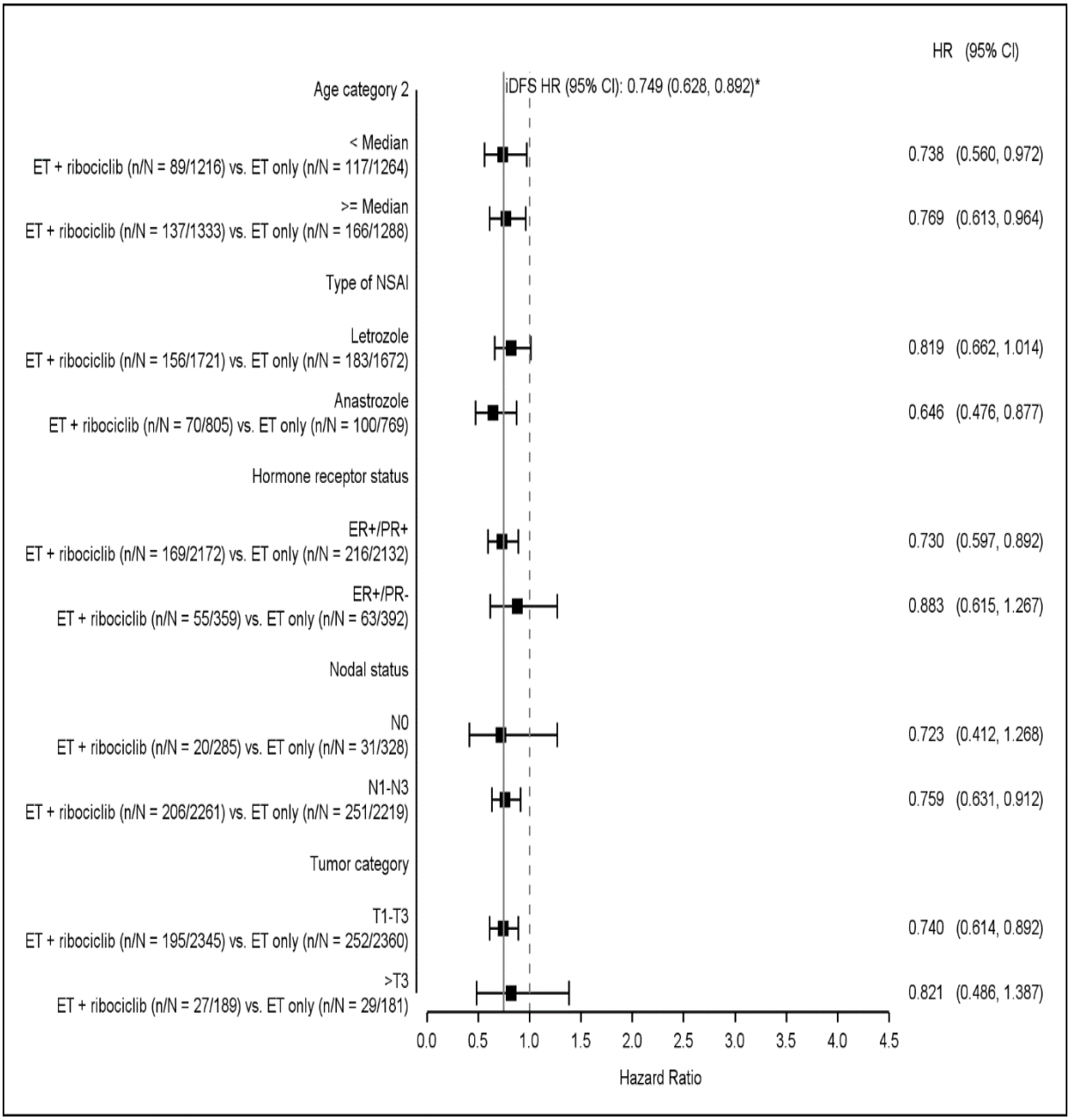
* Hazard rate in group ET + ribociclib versus hazard rate in group ET only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors. The group ET only is the reference in the hazard ratio calculation.

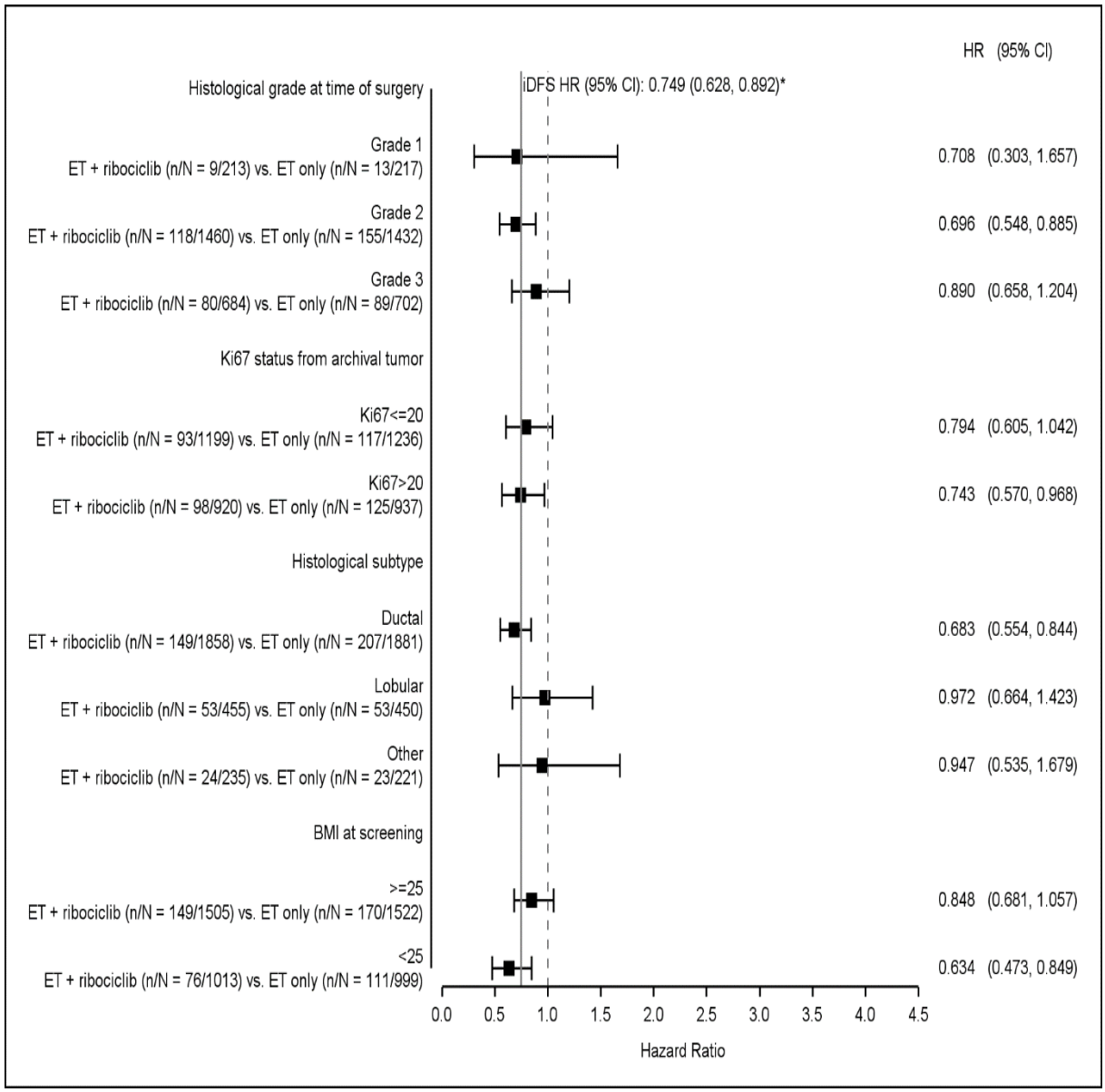
Source: [SCE Add. Study O12301C-Figure 3-7]

Figure 4: Forest plot of iDFS – subgroup analysis (final iDFS analysis, 21-Jul-2023 data cut-off (FAS)









NE=not evaluable.

*-Hazard rate in group ribociclib + ET versus hazard rate in group ET only is computed using the Cox proportional hazards model with treatment as a single covariate and premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world as stratification factors. Th group ET only is the reference in the hazard ratio calculation.

Source: [SCE Add. Study O12301C-Figure 3-8]

The Applicant's Position:

Subgroup analyses of iDFS (21-Jul-2023 cut-off) demonstrated a treatment benefit of ribociclib + ET across stratification factors of anatomic stage, prior (neo)adjuvant chemotherapy, menopausal status, and geographic region (Figure 3), as well as other predefined clinically relevant subgroups, including nodal status (Figure 4) [CO Study O12301C-Section 4.4.1].

The FDA's Assessment:

FDA agrees with the Applicant's assessment that a variety of exploratory subgroup analyses by sex, menopausal status, stage, prior therapy, and pathology results generally were supportive of the addition of ribociclib to ET with point estimates for the iDFS HR <1.

FDA emphasizes that NATALEE was not designed to formally test any secondary endpoints, including OS, and cannot support a labeling claim for the other efficacy endpoints but generally agrees with the Applicant's summary of the efficacy data for the secondary endpoints of RFS, DDFS, and OS. These secondary endpoint results are considered supportive of the iDFS benefit for the addition of ribociclib to ET. The endpoints of RFS and DDFS, which include events earlier than death, are clinically informative in view of the unexpectedly low number of deaths observed in NATALEE at the time of the final iDFS analysis.

Given that the number of deaths was lower than anticipated at the final iDFS analysis, prior to the sNDA submission, FDA requested that the applicant provide simulations to estimate the probability of OS detriment with addition of ribociclib to ET based on a total of 340 events projected to occur at end of study. Results of the simulation provided by the Applicant are shown in Table 18 below:

Table 18: Applicant's OS Simulation

True HR for future OS events	Mean est*.HR at 340 events (95% CI)	P(est.HR>1) (%)	P(est.HR>1.1) (%)	P(est.HR>1.2) (%)
0.892*0.7=0.624	0.752 (0.580, 0.976)	0	0	0
0.892*0.8=0.714	0.802 (0.618, 1.041)	0.3	0	0
0.892*0.9=0.802	0.849 (0.653, 1.103)	1.3	0.2	0
0.892	0.894 (0.688, 1.162)	7.3	0.3	0
0.892*1.1=0.981	0.937 (0.722, 1.217)	20.3	1.7	0.1
0.892*1.2=1.070	0.978 (0.753, 1.270)	37.3	5.9	0.4
0.892*1.3=1.160	1.017 (0.783, 1.321)	58.6	15.8	1.5

Source: Provided by Applicant

In addition, FDA requested an additional OS analysis with the 90-day safety update. At the 90-day safety update, with a data cutoff of October 26, 2023, there were a total of 91 (3.6%) deaths in the ribociclib + ET arm, and 98 (3.8%) deaths in the ET only arm. The OS HR was 0.88 (95% CI: 0.66, 1.17) for the ribociclib + ET arm vs the ET only arm.

Overall, results of OS at the time of final iDFS and at the 90-day safety update support that there appears to be no detriment in OS at this time with addition of ribociclib to ET. A postmarketing requirement (PMR) will be issued for the applicant to provide all additional OS analyses as prespecified in the protocol and SAP, including OS at the time of end of trial. This is discussed further in Section 13.

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported following Investigator site audits [Study O12301C Primary analysis CSR-Section 9.6.5.1].

The FDA's Assessment:

FDA inspected 5 clinical sites for NATALEE.

Table 19: FDA – Clinical Site Inspections

Site Contact	Site #	Pt #	Primary Endpoint Verification
Dr. Bozena Kukielka-Budny Doktora Kazimierza Jaczewskiego 7 LUBLIN, NA 20-090 Poland Phone: 48509518811 Email: bozena-budny@wp.pl	1810	84	Please ask inspector to verify all subjects in the investigational arm (patients who received ribociclib and endocrine therapy) who were reported as **not** having an iDFS event by July 21, 2023. Please audit 10% of the subjects in the investigational arm at each site reported to have an iDFS event by July 21st, 2023. If 50% of these positive events are misclassified, please verify all subjects in the investigational arm reported to have an iDFS event by July 21, 2023. Specifically, verify the iDFS Event Type (i.e. NPM, death, recurrence) and Date of Event. If time permits, please also audit 10% of the subjects on the control arm (patients who received endocrine therapy only) at each site reported to have an iDFS event and those without an iDFS event by July 21, 2023.
Dr. Zbigniew Nowecki I The Maria Sklodowska Curie Memorial Cancer Centre And Institute Of Oncology (Mcmcc) WARSAW, NA 02-78 Poland Phone: 48225462522 Email: zbigniew.nowecki@pib-nio.pl	1811	131	
Dr. Shaker Dakhil R 818 North Emporia Wichita, KS 67214 Phone: 3162624467 Email: shaker.dakhil@cancercenterofkansas.com	5007	21	
Dr. Priyanka Sharma 2330 Shawnee Mission Pkwy Westwood, KS 66205 Phone: 9135886029 Email: psharma2@kumc.edu	5057	25	

Site Contact	Site #	Pt #	Primary Endpoint Verification
Dr. Lowell Hart 3840 Broadway Fort Myers, FL 33901 Phone: 2392749930 Email: llhart@flcancer.com	5075	40	

Refer to Section 4.1 for further details on the findings of inspections. Complete information can be found in the FDA OSI review memo. Overall, no action was indicated for the sites.

Dose/Dose Response

The Applicant's Position:

Results of Study O12301C demonstrated that the 400 mg ribociclib dose is safe and efficacious for use for eBC in the adjuvant setting, where patients have a lower tumor burden than in the advanced or metastatic setting. Thus, the recommended dose of ribociclib for the adjuvant setting for eBC is 400 mg (two 200-mg film-coated tablets) of ribociclib once daily, Days 1 to 21 of each 28-day cycle for 3 years combined with 5 years of ET.

Dose reductions:

Recommended dose modification guidelines in the adjuvant setting are as follows:

- Starting dose 400 mg/day (two 200-mg tablets)
- Dose reduction 200 mg/day (one 200-mg tablet)

If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued [SCE Study O12301C-Section 4.2].

Dose justification: Both neutropenia and QTcF prolongation, the adverse events related to ribociclib PK exposure, are lower in eBC patients in Study O12301C at the dose of 400 mg than in aBC patients at the dose of 600 mg, supporting improved tolerability of the 400 mg dose in eBC patients. The PK-QT modeling confirmed the exposure-QTcF relationship in eBC patients, and patient population is a significant covariate where eBC patients showed less QTcF response than aBC patients.

Efficacy in patients with eBC was demonstrated by the statistically significant improvement of both the primary endpoint of iDFS and the secondary endpoints of RFS and DDFS. Due to limited sample size of patients with iDFS events, exposure-efficacy relationship cannot be characterized.

In conclusion, based on the observed efficacy and safety data of Study O12301C, exposure-response analysis, and the historical data in patients with aBC, 400 mg ribociclib (once daily for

3 weeks on/1 week off in a 28-day cycle) is demonstrated to be a safe and effective dose in patients with eBC.

The relationship between Ctrough concentration quartiles and iDFS events was examined for patients included in the PK-iDFS set; however, no conclusions could be drawn due to limited data [CO Study O12301-Sections 3.3 and 3.2.1.1].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. Refer to FDA's clinical pharmacology review in Section 6.3.2.

Durability of Response

The Applicant's Position:

At the final iDFS analysis a substantial majority of patients, 1996 (78.3%) in the ribociclib + ET group, had discontinued ribociclib, with 1091 patients (42.8%) having completed 3 years of ribociclib treatment per protocol [SCE Add. Study O12301C-Section 3.1]. As of the data cut-off date of 21-Jul-2023 for the final iDFS analysis, there were approximately 5.6 months of additional follow-up for iDFS, with median duration of iDFS follow-up (from randomization to last recurrence assessment) of 33.3 months for both arms [SCE Add. Study O12301C-Section 3.2.1].

The statistically significant improvement in iDFS in the ribociclib + ET arm compared with the ET only arm seen at IA3 was further confirmed with more mature data at final iDFS analysis.

With longer follow-up, additional iDFS events, and a larger proportion of patients completing the 3-year treatment regimen of ribociclib, the hazard ratios were very similar when comparing results from the second and third interim analyses, as well as the final iDFS analysis. These results reflect the stability of the data over time. In addition, the confidence intervals are narrowing, indicating that the data are becoming more mature. These results indicate that although the study is ongoing, it is not expected that the overall assessment of the benefit:risk of ribociclib in eBC would change [CO Study O12301C-Section 4.5.1].

The FDA's Assessment:

As noted in Section 8.1, the majority of iDFS events in HR+, HER2-negative early breast cancer occur in years 5-20+ after diagnosis. It would be very unlikely for the overall assessment of the benefit-risk of ribociclib to become unfavorable over time given the trend in iDFS HRs observed to this point; however, the impact of ribociclib on late recurrences cannot be determined from the available data with the current duration of follow-up. A PMC to provide further OS data is discussed in Section 13.

Persistence of Effect

The Applicant's Position:

The persistent, beneficial effect of ribociclib on the primary iDFS endpoint was further supported by a series of subgroup analyses. Consistency of the iDFS improvement was generally evident across all subgroups assessed for both the primary and final iDFS analyses, including stratification factors (anatomic stage, prior (neo)adjuvant chemotherapy, menopausal status, geographic region), and other predefined clinically relevant subgroups, demonstrating the validity of the results across the broad study population, with no particular subgroup driving these results.

Results for secondary endpoints, including RFS and DDFS were also consistent with and supportive of the iDFS primary endpoint results.

At the final iDFS analysis, ribociclib demonstrates persistent efficacy in patients with HR-positive, HER2-negative, Stage II and III eBC with continued separation of the KM curves, consistent HRs between the primary and final iDFS analyses, and narrower confidence intervals across the primary and secondary endpoints [CO Study O12301C-Section 4.5.2]

The FDA's Assessment:

While there was no alpha spending on efficacy endpoints other than iDFS or on analysis of iDFS in these subgroups, and therefore these results cannot support any labeling claims, FDA agrees that the results of subgroup analyses and analysis of secondary endpoints were supportive of the results of the primary iDFS analysis in the ITT population.

FDA requested that the Applicant conduct an additional OS analysis with the 90-day safety update. As of the data cutoff of October 26, 2023, there had been 91 deaths in 2549 patients in the ribociclib + ET arm compared to 98 deaths in 2552 patients in the ET only arm. Median OS was not reached in either arm. The OS HR was 0.88 (95% CI: 0.66, 1.17). A PMC will require the Applicant to submit pre-specified OS analyses, including the results of OS at the planned end of the study, as discussed in Section 13.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Patient-reported outcomes (11-Jan-2023 cut-off)

Overall, treatment with ribociclib + ET maintained HR QoL scores over time, further supporting the clinical benefit of the proposed treatment regimen in the target population.

In general, the primary QoL measure of interest, EORTC QLQ-C30 physical functioning, of patients treated with ribociclib + ET was similar to that of patients treated with ET only. Physical functioning scores were generally similar between the two treatment arms throughout the study, with no meaningful differences at any post-baseline timepoint through to EOT.

Furthermore, PRO scores in the ribociclib + ET arm, upon treatment, remained within 0.5 SD of their baseline scores.

A longitudinal analysis of differences in physical functioning score between treatment arms using a repeated measures model (RMM) revealed no substantial or meaningful effect of treatment or treatment by time interaction on the physical functioning scores of EORTC QLQ-C30. In addition, results for the RMM were generally consistent with the change from baseline analyses and related time profile for physical functioning.

Analysis of mean change from Baseline scores of global health status/QoL, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scores of the EORTC QLQ-BR23, the VAS scores of the EQ-5D-5L, and the anxiety domain and depression domain scores of HADS indicated no meaningful differences between treatment arms over time.

Results of the RMM for health status/QoL, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scores of the EORTC QLQ-BR23, the VAS scores of the EQ-5D-5L, and the anxiety domain and depression domain scores of HADS confirmed that there was no evidence of a difference between treatment arms during the treatment period [CO Study O12301C-Section 4.3.2].

The FDA's Assessment:

FDA reviewed the PRO results submitted by the Applicant but did not independently verify all of the results. PRO data were collected at screening, every 12 weeks (±2 weeks) after randomization during the first 24 months and every 24 weeks (±2 weeks) thereafter, at EOT, at confirmation of first recurrence, at confirmation of distant recurrence (if the first recurrence was not a distant recurrence), and during the first 12 months after confirmation of distant recurrence (every 12 weeks [±2 weeks] if confirmation of distant recurrence happened during the first 24 months after date of randomization or every 24 weeks [±2 weeks] if confirmation of distant recurrence happened after the first 24 months after the date of randomization).

In terms of data quality, from baseline through EOT, the compliance rate was >80% in both arms.

The PRO results from this study cannot support any efficacy claims as PRO assessment was sparse, and there was no plan for formal testing of any PRO endpoints. FDA does not agree with the statement that the PRO results support the clinical benefit of the proposed treatment regimen in the target population as this study was not designed to support such conclusions. Furthermore, there was no observed difference in patient reported disease symptoms (e.g., breast cancer symptom scores of the EORTC WLW-BR23), which does not support the Applicant claim of clinical benefit based upon PROs.

Lastly, the PRO strategy lacked a comprehensive tolerability assessment including side effects of treatment and overall side effect impact. No post-baseline PRO assessment occurred until week 12, obscuring important tolerability information.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA conducted exploratory subgroup analyses of iDFS by anatomic stage and nodal status (Anatomic Stage IIA [Node+ and Node-], Anatomic Stage IIB, and Anatomic Stage III. Results are presented below.

Table 20: FDA – Final iDFS by Anatomic Stage and Nodal Status

	Ribociclib + ET Number of Events/N	ET Only Number of Events/N	HR (95% CI)
Anatomic Stage IIA	15/480	32/521	0.48 (0.26, 0.89)
Node positive	4/268	12/280	0.31 (0.10, 0.96)
Node negative	11/212	20/241	0.65 (0.31, 1.36)
Anatomic Stage IIB	40/531	48/513	0.82 (0.54, 1.26)
Anatomic Stage III	170/1528	203/1512	0.76 (0.62, 0.93)

Source: FDA Analysis

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

Not applicable. The Applicant submitted a single trial NATALEE conducted in the adjuvant setting. Ribociclib is already FDA-approved for adults with advanced or metastatic HR+, HER2-negative breast cancer in combination with fulvestrant or an aromatase inhibitor.

8.1.4 Assessment of Efficacy Across Trials

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable. The Applicant submitted a single trial NATALEE conducted in the adjuvant setting.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable. The Applicant submitted a single trial NATALEE conducted in the adjuvant setting.

8.1.5 Integrated Assessment of Effectiveness

The Applicant's Position:

At the final iDFS analysis (509 events, DCO 21-Jul-2023), the addition of ribociclib to ET continued to show a statistically significant and clinically superior efficacy for iDFS, using STEEP criteria as per Investigator assessment, compared with ET only. The median duration of iDFS follow-up between randomization and the data cut-off date was 33.3 months, representing an additional 5.6 months of iDFS follow up since the primary analysis.

- Based on a stratified Cox regression analysis, there was an estimated 25.1% relative reduction in the risk of an iDFS event (hazard ratio = 0.749; 95%CI: 0.628, 0.892 (one-sided stratified log-rank test nominal p-value = 0.0006).
- The iDFS rate at 3 years is 90.7% (89.3%, 91.8%) for ribociclib + ET vs. 87.6% (86.1%, 88.9%) for ET only, representing a 3.1% absolute benefit in favor of ribociclib + ET.
- Consistency of the iDFS improvement was generally evident across all subgroups assessed, including key subgroups (anatomic staging, menopausal status, nodal involvement), demonstrating the validity of the results across the broad study population.
    - Stage III – hazard ratio = 0.755 (95% CI: 0.616, 0.926); Stage II – hazard ratio = 0.700 (95% CI: 0.496, 0.986)
    - Premenopausal women & Men – hazard ratio = 0.688 (95% CI: 0.519, 0.913); Postmenopausal – hazard ratio = 0.806 (95% CI: 0.645, 1.007)
    - N0 subgroup – hazard ratio = 0.723 (95% CI: 0.412, 1.268); N1-N3 subgroup – hazard ratio = 0.759 (95% CI: 0.631, 0.912)
- A statistically significant improvement in RFS was demonstrated for the ribociclib + ET arm compared with the ET only arm; RFS HR is 0.727, 95% CI (0.602,0.877) (nominal p-value = 0.0004), with an estimated 27.3% relative reduction in the risk of RFS per Cox regression model.
- A statistically significant improvement in DDFS was demonstrated for the ribociclib + ET arm compared with the ET only arm: DDFS HR is 0.749, 95% CI (0.623,0.900) (nominal p-value = 0.0010), with an estimated 25.1% relative reduction in the risk of DDFS per Cox regression model.
- There was an estimated 26.2% relative reduction in the risk of DRFS for patients in the ribociclib + ET arm (hazard ratio = 0.738; 95% CI: 0.606, 0.898) (nominal p-value =

0.0012). The 3-year DRFS rates at the final iDFS analysis (DCO 21-Jul-2023) were 92.6% (95% CI: 91.4, 93.7) in the ribociclib + ET arm and 90.1% (95% CI: 88.7, 91.3) in the ET only arm, reflecting a 2.5% absolute benefit favoring ribociclib + ET.

- Although the OS data were still immature, there was no detrimental effect on OS for the final iDFS analysis.

With this final iDFS analysis, a substantial majority of patients have completed 3 years of treatment, and efficacy has been sustained as demonstrated by continued separation of the KM curves, consistent HRs and narrower confidence intervals across the primary and secondary endpoints. This further confirms the benefit for a broad population of eBC patients receiving ribociclib for a 3-year duration [SCE Add. Study O12301C-Section 6].

The FDA's Assessment:

NATALEE was a randomized (1:1) multicenter trial for the adjuvant treatment of patients with HR+, HER2-negative stage II and III early breast cancer. Patient were randomized to receive ribociclib (400 mg daily 3 weeks on/1 week off for 3 years) + endocrine therapy (ET, non-steroidal aromatase inhibitor [NSAI], as well as goserelin in men and premenopausal women, dosage per SOC for 5 years) vs. ET only.

The primary endpoint of NATALEE was invasive disease-free survival (iDFS) by investigator assessment in the intent to treat (ITT) population. A total of 2549 patients were randomized to the ribociclib + ET arm and 2552 patients to the ET only arm. NATALEE met its primary endpoint of iDFS at IA3 demonstrating a statistically significant improvement in iDFS (hazard ratio [HR] 0.748, 95% confidence interval [CI] 0.619-0.906). The 3-year iDFS was 90.4% (88.6-91.9) on the ribociclib + ET arm compared to 87.1% (85.3-88.8) on the ET only arm, for an absolute difference of 3.3%. However, at IA3, due to a large amount of censoring for iDFS with only 20% of patients having completed 3 years of adjuvant ribociclib and immature OS with 134 total deaths (OS HR 0.759, 95% CI 0.539-1.068), FDA advised the Applicant to continue to follow participants until the final iDFS analysis.

The sNDA submission for 209092/S-018 was received on December 22, 2023, and the Applicant used a priority review voucher (PRV). The sNDA submission for 209935/S-027 (co-pack) was received on March 11, 2024, and cross-references sNDA 209092/S-018. The sNDA submission is based on final iDFS, with a data-cutoff date of July 21, 2023. At final iDFS analysis, the HR was 0.75 (95% CI 0.63-0.89). While the median iDFS was not estimable on either treatment arm, the 3-year iDFS rates were 90.7% (95% CI: 89.3, 91.8) in the ribociclib + ET arm and 87.6% (95% CI: 86.1, 88.9) in the ET only arm. The interim OS analysis at the time of final iDFS analysis was immature with 84 deaths (3%) on the ribociclib + ET arm and 88 deaths (3%) on the ET only arm. The OS HR was 0.89 (95% CI 0.66-1.20) with median OS not estimable.

As of the July 21, 2023 data cut-off, 43% of patients had completed 3 years of ribociclib + ET, and 69% had completed ≥2 years of ribociclib + ET. There were 172 total deaths on

study as of the final iDFS analysis. On-treatment deaths were uncommon overall, but higher on the ribociclib + ET arm, 20 deaths (0.8%) compared to 9 deaths (0.4%) on the ET only arm, and more often due to adverse events.

The 90-day safety update submitted on March 21, 2024 had a data-cut off of October 26, 2023 and provided approximately 3 additional months of information. At the safety update, there continued to be fewer overall deaths on study in the ribociclib + ET arm: 83 (3.3%) in the ribociclib + ET group and 89 (3.6%) in the ET only group, most of which were attributed to disease progression.

Overall safety findings were consistent with the original submission and the known safety profile of ribociclib + ET as reflected in the current USPI.

8.2 Review of Safety

The Applicant's Position:

The key safety data in support of this application are from the primary and final iDFS analyses of Study O12301C. In this large study (N=5101, FAS; N=4968; Safety set), ribociclib 400 mg in combination with standard adjuvant ET (AI; anastrozole or letrozole) is compared with standard of care adjuvant ET alone. The population enrolled in this study reflects the target population of adult patients (including pre- and postmenopausal women plus men) with HR-positive, HER2-negative, Stage II or Stage III eBC who are at risk of recurrence [SCS Study O12301C-Section 1.1.2]. Based on the Safety set, this study population consists of patients with anatomic Stage II (40.3%) or Stage III (59.4%) disease as per AJCC staging (eighth ed.) who had completed surgery, followed by chemotherapy, and/or radiotherapy with curative intent.

In view of the stratification (by menopausal status, anatomic stage group, use of prior neoadjuvant/adjuvant chemotherapy, and geographic region), 1:1 randomization, and balanced demographic and disease characteristics between the two arms, comparisons between the ribociclib + ET and ET only groups allow for valid assessment of safety in this population. This population is also considered appropriate for the detection and characterization of AEs and to provide guidance on toxicity management [CO Study O12301C-Section 5.1.1].

The FDA's Assessment:

FDA agrees with the Applicant's characterization of the safety population. The stratification criteria are appropriate for the population studied. The population enrolled includes sufficient numbers of patients with Stage II (approximately 40%) and III (approximately 60%) breast cancer to support the proposed indication. Baseline characteristics were well-balanced. Overall, the NATALEE participants, of whom 88% had N1-N3 disease, <10% had grade 1 disease, and 87% received (neo)adjuvant chemotherapy, represent a markedly higher risk subset of the broader US population of patients with HR+, HER2-negative early breast cancer; therefore, the efficacy and safety results of this study should not be extrapolated to a lower-risk population of patients.

Black or African-American patients, who are more likely to be diagnosed with high-risk early breast cancer than patients of other races, and more likely to experience recurrence or death after a diagnosis of early breast cancer, are extremely under-represented in the NATALEE trial. A postmarketing commitment (PMC) to provide data from ongoing/planned clinical trials or other data sources to better characterize the efficacy and safety of ribociclib in racial minority subgroups, including Black or African-American patients, is planned as discussed in Section 13.

8.2.1 Safety Review Approach

The Applicant's Position:

The key safety data include results for the 4967 patients with eBC in the Safety set of Study O12301C who received study treatment based on the final iDFS analysis (DCO of 21-Jul-2023). The final iDFS analysis was conducted after 40.3 months of median study follow-up, when

patients were treated for a median duration of 36 months in both arms, with an additional 6.3 months of study follow-up from the primary analysis.

Additionally, long-term safety has already been established for the ribociclib 600 mg starting dose in the aBC setting for a pool of 1065 patients from Studies LEE011A2301, LEE011E2301 (excluding patients treated with tamoxifen), and LEE011F2301 based on a total exposure of 2262 patient-years. These pooled safety data provide further context for the safety of ribociclib at 400 mg in patients with eBC.

Novartis considers the body of evidence based on Study O12301C as substantial to assess the ribociclib safety profile in patients with HR-positive, HER2-negative, eBC in the context of the known and established safety profile at 600 mg in the aBC setting (pooled aBC dataset = 1,065 patients exposed to ribociclib with an estimated exposure of 2081 patient-years [Study A2301 SCS Add.-Table 1-8]).

The known important identified risks with ribociclib remain as: Myelosuppression, Hepatobiliary toxicity, QT interval prolongation, and Reproductive toxicity. One important potential risk with ribociclib is Renal toxicity. These are discussed in detail in [CO Study O12301C-Section 5.3] [SCS Add. Study O12301C-Section 2.6] and [SCS Study O12301C-Section 2.6].

The FDA's Assessment:

The size of the safety population from the NATALEE trial (N=4967) is appropriate for a trial conducted in the adjuvant setting. The safety data from the NATALEE trial, especially within the context of a well-characterized AE profile from multiple prior studies of ribociclib + ET in the metastatic setting and 7.5 years of postmarketing experience, is adequate for benefit-risk assessment of ribociclib in a curative intent population.

FDA generally agrees with the Applicant's assessment of the most important adverse events of special interest (AESI) as discussed later in the review with one addition. The risk of both SARS-CoV-2 infection and deaths attributed to COVID-19/COVID-19 pneumonia was increased in patients who received ribociclib + ET. This is discussed in further detail in Section 8.2.4.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 21: Duration of exposure to study treatment by group in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 data cut-off	
	Ribociclib + ET N=2525	ET only N=2442
Adherence	**n (%)**	**n (%)**
Duration of exposure		
0 to < 3 months	122 (4.8)	167 (6.8)
3 to < 6 months	84 (3.3)	79 (3.2)
6 to < 9 months	58 (2.3)	50 (2.0)
9 to < 12 months	48 (1.9)	54 (2.2)
12 to < 15 months	40 (1.6)	45 (1.8)

	Final iDFS analysis: 21-Jul-2023 data cut-off	
	Ribociclib + ET N=2525	ET only N=2442
Adherence	**n (%)**	**n (%)**
15 to < 18 months	33 (1.3)	44 (1.8)
18 to < 21 months	45 (1.8)	56 (2.3)
21 to < 24 months	33 (1.3)	35 (1.4)
24 to < 27 months	25 (1.0)	28 (1.1)
27 to < 30 months	285 (11.3)	259 (10.6)
30 to < 33 months	124 (4.9)	126 (5.2)
33 to < 36 months	341 (13.5)	290 (11.9)
≥ 36 months	1287 (51.0)	1209 (49.5)
Duration of exposure (mo)		
Mean	32.8	31.9
SD	12.83	13.66
Minimum	0	0
Median	36.2	35.9
Maximum	54	54
Patient years	**6904.3**	**6487.3**

Source: [SCS Add. Study O12301C Table 1-2]

The Applicant's Position:

The duration and extent of study treatment exposure was considered adequate to assess the ribociclib safety profile in this patient population with HR-positive, HER2-negative, eBC.

At the final iDFS analysis, the median duration of exposure was 36.2 months (range: 0 to 54) for ribociclib + ET treatment vs. 35.9 months (0 to 54) for ET only treatment. A total of 1228 patients (48.6%) had 33 months or longer of ribociclib exposure. A total of 1628 patients (64.5%) had 33 months or longer of study treatment exposure in the ribociclib + ET group, which includes the last dosing visit of the 3-year ribociclib regimen.

The total exposure to study treatment was 6904.3 patient-years for the ribociclib + ET treatment group (N=2525) and 6487.3 patient-years for the ET only treatment group (N=2442). Importantly, the difference since IA3 was +1018.4 patient-years in the ribociclib + ET group. By each drug component, ribociclib exposure was 5352.1 patient-years (N=2525); NSAI exposure was 6879.1 patient-years in the ribociclib + ET group vs. 6467.5 patient-years in the ET only group (N=4967).

The median relative dose intensity (RDI) for ribociclib was 94.0% (range: 14 to 132), and the median RDI for NSAI in both the ribociclib + ET and ET only groups was 100%, indicating the addition of ribociclib continued to not affect the tolerability of NSAI/ET.

Generally, ribociclib dose reduction/interruption occurred early during study treatment administration. Dose adjustments (interruptions and reductions) of ribociclib were allowed for safety concerns per guidelines presented in the study protocol. Dose reductions of ribociclib occurred in 26.7% of patients and were primary attributable to AEs (22.8%). Dose interruptions of ribociclib occurred in 86.1% of patients and were also primarily attributable to AEs (66.2%). Dose interruptions for NSAI/AI occurred in 44.5% of patients in the ribociclib + ET arm, and in

35.7% of patients in the ET only arm. Overall, the primary reasons for dose adjustments were AEs.

Discontinuation of ribociclib (reported for 78.3% of patients) was primarily due to completion of ribociclib treatment (42.8%), followed by AE (19.5%). Generally, ribociclib discontinuation due to AEs also occurred early during study treatment administration [SCS Add. Study O12301C-Section 1.2.1].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. As of the July 21, 2023 data cut-off, 82% of participants had completed >24 months of ribociclib + ET and approximately half had completed a full 36 months of treatment.

The dose of ribociclib used in the NATALEE trial (400 mg daily) is lower than the dose in the metastatic setting (600 mg daily), and ribociclib was better tolerated in the adjuvant setting than in prior metastatic trials. In spite of a lower starting dose, dose modification of ribociclib, however, remained common. In total, 86% had treatment interruption, mostly for adverse reactions, more than one-quarter of participants required ribociclib dose reduction, and one in five patients discontinued due to an AE. On trial, discontinuations due to AE occurred in the first few months of treatment, and many of these were based upon laboratory abnormalities. Outside of a clinical trial, these early adverse reactions and need for one or more treatment interruptions may result in decreased patient adherence to ribociclib given that the treatment is self-administered to patients with no evidence of disease.

The adverse reactions of ribociclib and ET are largely non-overlapping, and thus despite the increased toxicity resulting from addition of CDK 4/6 inhibitor to endocrine therapy, interruptions of endocrine therapy were only 9% more common in the ribociclib + ET arm, indicating that addition of ribociclib did not significantly compromise ability to deliver the known effective adjuvant endocrine therapy. AI-induced musculoskeletal symptoms (AIIMS) are among the most common tolerability issues that result in interruption or discontinuation of AIs in clinical practice. Based on FDA's analysis of musculoskeletal pain as a grouped term, these AEs occurred in 56% (1.5% grade 3) of those on ribociclib + ET versus 58% (1.8% grade 3) on ET only, and therefore were not increased with the addition of ribociclib to AI.

Relevant characteristics of the safety population:

Data:

Table 22: Overview of clinical studies with safety data

Key feature	Study O12301C
Controlled study	Yes
Phase	III
Study design // endpoints	Open-label, multicenter, randomized, active-controlled vs. standard-of-care // Efficacy, PK, safety, tolerability, exploratory.
Population	Salient demographic data

Key feature	Study O12301C
	North America/Western Europe/Oceania[1] region=3032 patients Premenopausal women and men=2193 patients (based on eCRF stratum) Yes, had prior chemotherapy=4309 patients (based on eCRF stratum) Age: median=52.0 y (range: 24 to 90); ECOG PS score 0=83.1% Salient diagnostic data AJCC Stage II (40.3%) or Stage III (59.5%) Predominant histology: invasive ductal carcinoma NOS=73.0%. Prior mastectomy=65.7%. At diagnosis: G1=9.0%, G2=57.3%, G3=20.7%; N0=28.1%, N1=41.0%, N2=12.3%, N3=6.2%; Ki67 at diagnosis: median score=20.0; categories: ≤ 14%=20.0%, > 20%=36.8%. Surgical specimen: G1=8.4%, G2=56.8%, G3=27.0%; N0=15.7%, N1=41.3%, N2=27.8%, N3=15.0%; Ki67 of surgical specimen: median score=15.0; categories: ≤ 14%=22.0%, > 20%=18.1%.
Treatment duration (fixed-term as adjuvant treatment)	Ribociclib (36 mo) plus ET (at least 60 mo) ET only: at least 60 mo
No. of patients (N) treated	**4968**
No. (n) by treatment combination	Ribociclib (400 mg) plus ET: 2524 (female=2514; male=10, 0.4%) ET only: 2444 (female=2435; male=9, 0.4%)
Relevant entry criteria (key only)	
Age, sex	≥ 18 years: females with known menopausal status; males
Disease/stage	HR-positive, HER2-negative, Stage II or Stage III eBC, irrespective of nodal status
Inclusion criteria	May have received any standard neoadjuvant and/or adjuvant ET upon ICF signing: randomization should have occurred within 12 mo of initial start date of ET. Of note: ovarian suppression or short-term ET (fertility preservation) was not considered neoadjuvant/adjuvant ET. If tamoxifen or toremifene received: washout as 5 half-lives (35 d) prior to randomization. By centralized 12-lead ECG: Screening QTcF < 450 ms; resting heart rate ≥ 50 to ≤ 90 bpm.
Exclusion criteria	Clinically significant, uncontrolled HD, and/or cardiac repolarization abnormality, included: history of documented MI, angina pectoris, symptomatic pericarditis, coronary artery bypass graft within 6 mo of study entry; documented cardiomyopathy; LVEF < 50% (by optional MUGA or ECHO); long QT syndrome, family history of idiopathic sudden death, congenital long QT syndrome; clinically significant cardiac arrhythmia, complete left bundle branch block, high-grade AV block; or uncontrolled arterial HTN with systolic BP > 160 mm Hg.
Status // milestone	Ongoing // First-patient-first-visit (FPFV): 07-Dec-2018; DCO: 11-Jan-2023

At enrollment, population was controlled to ~40% Stage II.
[1]Only patients from Australia were enrolled within the Oceania geographical region.

Source: [SCS Study O12301C Table 1-2]

The FDA's Assessment:

Only 16% of the NATALEE study population was enrolled from the United States. Therefore, it is important to assess whether the results of the trial can be generalized to a U.S. population. The median age of 52 with a range of 24 to 90 is representative of the demographics of HR+, HER2-negative breast cancer in the U.S. The patient population includes robust representation of patients with stage II (~40%) and stage III (~60%) disease, as well as a range of menopausal status; however, as noted earlier in the review, the NATALEE population was much higher risk than the broader US population with HR+, HER2-negative early breast cancer as 87% of participants had received (neo)adjuvant chemotherapy and only 12% had N0 disease.

There were only 19 male patients enrolled in NATALEE, which is a limitation for the assessment of efficacy and safety/tolerability by sex, but their inclusion is important given

the rarity of the condition and the presently inadequate access to investigational agents and limited evidence base for male breast cancer.

Despite typically having a higher stage at presentation and a greater risk of recurrence or death after early breast cancer in the U.S. population, Black or African-American patients are significantly under-represented in NATALEE. Only 1.7% of participants (n=86, of whom 41 were randomized to receive ribociclib + ET) were Black or African-American. As a result, the NATALEE trial contains only 118 patient-years of experience with ribociclib + ET in Black patients with early breast cancer compared to 5116 patient-years of experience with the combination in white patients.

Sixty percent of participants had tumors that were stage III, 88% were N1-N3, 87% had received (neo)adjuvant chemotherapy, and very few were grade 1, which reflects a substantially higher risk population than most patients in the U.S. with HR+, HER2-negative early breast cancers. The benefit-risk assessment of adjuvant ribociclib based on the NATALEE trial should therefore not be extrapolated to a more typical lower-risk US population of patients with early-stage HR+, HER2-negative breast cancer.

As noted in Table 22 above, patients with a variety of cardiac conditions were excluded from NATALEE. These conditions are not rare in the U.S., especially in the older adults who represent the majority of patients with HR+, HER2-negative breast cancer. Clinicians should counsel patients with pre-existing cardiac conditions regarding the limitations of the NATALEE safety data and consider whether treatment with ribociclib is appropriate and whether more routine monitoring of ECGs beyond 4 weeks is warranted.

In addition, the majority of patients in NATALEE (83%) were ECOG performance status 0, and 17% were ECOG 1. Patients with ECOG ≥2 were excluded from the trial. The safety of ribociclib in the adjuvant setting for patients with poorer performance status or other comorbid conditions may differ.

Adequacy of the safety database:

The Applicant's Position:

Novartis considers the body of evidence based on Study O12301C as substantial to assess the ribociclib safety profile in patients with HR-positive, HER2-negative, eBC in the context of the known and established safety profile at 600 mg in the aBC setting (pooled aBC dataset = 1065 patients exposed to ribociclib with an estimated exposure of 2081 patient-years) [Study A2301 SCS Add.-Table 1-8].

The key safety data in support of this application are from the primary and final analysis of Study O12301C. In this large study (N=5101, FAS; N=4968; Safety set), ribociclib 400 mg in combination with standard adjuvant ET (AI; anastrozole or letrozole) is compared with standard of care adjuvant ET alone. The population enrolled in this study reflects the target population of adult patients (including pre- and postmenopausal women plus men) with HR-positive, HER2-negative, Stage II or Stage III eBC who are at risk of recurrence. Based on the Safety set, this study population consists of patients with anatomic Stage II (40.3%) or Stage III (59.4%) disease as per AJCC staging (eighth ed.) who had completed surgery, followed by chemotherapy, and/or radiotherapy with curative intent [CO Study O12301-Sections 5.1.1 and 5.1.2].

As of the 21-Jul-2023 cut-off date, 1091 patients (42.8%) in the ribociclib + ET group have completed the 3-year ribociclib treatment duration per protocol, with 69.4% having completed at least 2 years of ribociclib treatment, based on all patients randomized to the ribociclib + ET group (FAS). The safety follow-up in Study O12301C in terms of patient-years of exposure was 6904.3 patient-years for the ribociclib + ET group vs. 6487.3 patient-years for the ET only group, or an additional 1018.4 patient-years since IA3 [SCS Add. Study O12301C-Section 1.2.1]. These data show that the level of safety follow-up completed in the study thus far is adequate to detect any signals that are related to the safety profile of ribociclib, including those that are not dose-dependent and/or rare events, and is unlikely to change substantially with longer follow-up [CO Study O12301-Section 6.3.1.1].

The FDA's Assessment:

FDA agrees that the NATALEE trial is adequate to characterize the benefits and risks of ribociclib to endocrine therapy in adults with high-risk stage II and III HR+, HER2-negative breast cancer, but notes that the majority of stage II disease was based upon tumor size as only 12% of participants had N0 disease. The size of the safety population is typical for an adjuvant breast cancer trial; however, the sample size may not be adequate to detect rare adverse events in the adjuvant setting.

The majority of known adverse reactions related to ribociclib occurred on active treatment and resolved with treatment discontinuation, and therefore the duration of follow-up, which includes the full treatment period in the majority of patients as of the 90-day safety update, is acceptable to characterize adverse reactions with the following caveat. Given that patients with HR+, HER2-negative early breast cancer are being treated with curative intent, with a life expectancy measured in years to decades, the limited period of follow-up is not informative about the risk of late post-treatment adverse events, including secondary malignancy.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and adverse event databases were consistent.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. An audit of randomly selected case report forms by the clinical safety reviewer did not identify any data integrity concerns.

FDA inspected three U.S. and two foreign clinical trial sites for NATALEE. Per the inspectors, the NATALEE trial appears to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of this sNDA. The overall assessment was that no action was indicated. Results of the inspections are discussed in further detail above in Section 4.1. Full details are available in the FDA OSI review.

Categorization of Adverse Event

The Applicant's Position:

The safety evaluations were conducted on the overall Safety set (N=4968) for Study O12301C. The safety of ribociclib in combination with ET (plus goserelin in premenopausal women plus men), was evaluated on the basis of the following:

- Frequency, type, severity, and causal relationship of AEs to study treatment: AEs were graded according to the CTCAE v4.03 for all studies used in this safety assessment.
- Frequency of deaths, serious adverse events (SAEs), and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction)
- Frequency and type of AEs in key demographic subgroups (including sex, race, menopausal status at baseline, age group (< 65 years vs. ≥ 65 years) at baseline) and by Baseline disease characteristics
- Changes in laboratory variables, with particular attention to grade 3/4 laboratory abnormalities
- Electrocardiogram (ECG) changes

Based on its clinical relevance, the on-treatment period was redefined taking the 36-month treatment period for ribociclib into account, to include a maximum of 36 months plus 30 days in either study group.

Adverse events were coded using MedDRA version 25.1 [Study O12301C Primary Analysis CSR], [SCS Study O12301C] and MedDRA version 26.0 [Study O12301C EA&SU], [SCS Add. Study O12301C].

The FDA's Assessment:

FDA agrees with Applicant's description of AE categorization and the clinical relevance of the approach to analysis of ribociclib safety in the adjuvant setting. The definition of the on-treatment death period of 36 months of investigational product (IP) administration plus 30 days after last dose of treatment is appropriate given the study drug half-life of <2 days.

Routine Clinical Tests

The Applicant's Position:

Safety assessments included the regular monitoring of hematology, blood biochemistry, and coagulation (at Screening) performed at local laboratories. Laboratory data summaries included all assessments available from samples collected no later than 30 days after the last study treatment administration date.

Laboratory values converted to the International System of Units (SI) were analyzed using the CTCAE grading, and notable abnormal values were summarized for both hematology and blood biochemistry. The calculation of CTCAE grades was based on observed laboratory values only: clinical assessments were not considered. The severity grade of 0 was assigned for all non-missing values if a value was within normal laboratory limits for that parameter; grade 5 was not used. For laboratory tests where grades were not defined by CTCAE, results were categorized as

a low/normal/high classification(s) based on the normal laboratory range. The grading and criteria to define all laboratory toxicity grades were assigned programmatically by the coding dictionary.

Safety assessments included the monitoring of vital signs, including height (Screening only) and weight, body temperature, heart rate, and BP at the site during the in-person visit(s); and 12-lead ECG performed at the local and/or central laboratories. ECG data were read both locally and centrally. The analyses were based on central ECG assessments as all local data were read centrally. Heart rate, QT interval, and QTcF were assessed [SCS Study O12301-Section 1.1.3.6 and 1.1.3.7].

The FDA's Assessment:
FDA agrees with Applicant's description and approach to analysis of routine clinical tests.

8.2.4 Results

Deaths

Data:

Table 23: On-treatment deaths in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 data cut-off	
Category **Preferred term**	**Ribociclib + ET** **N=2525** **n (%)**	**ET Only** **N=2442** **n (%)**
No. pts who died on treatment	**20 (0.8)**	**9 (0.4)**
Primary reason: disease recurrence/progression	9 (0.4)	4 (0.2)
Primary reason: adverse event	11 (0.4)	4 (0.2)
Primary reason: other	0	1 (< 0.1)
Death	0	1 (< 0.1)
SAEs with fatal outcome	11 (0.4)	4 (0.2)
Brain oedema	1 (< 0.1)	0
COVID-19	3 (0.1)	1 (< 0.1)
COVID-19 pneumonia	3 (0.1)	0
Cardiac arrest	1 (< 0.1)	0
Cardiac failure congestive	0	1 (< 0.1)
Cardiopulmonary failure	1 (< 0.1)	0
Epilepsy	1 (< 0.1)	0
Ischaemic cardiomyopathy	0	1 (< 0.1)
Myocardial infarction	0	1 (< 0.1)
Pulmonary embolism	2 (0.1)	0
Respiratory failure	0	1 (< 0.1)
Road traffic accident	1 (< 0.1)	0
Sepsis	0	1 (< 0.1)
Treatment-related SAEs with fatal outcome	**1 (< 0.1)**	**0**

On-treatment deaths are defined as occurring on or after treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation.
MedDRA Version 26.0 has been used for reporting.

Source: [SCS Add. Study O12301C Table 2-7]

The Applicant's Position:

All deaths: As of the final iDFS analysis DCO, 172 deaths were reported during the study: 83 (3.3%) in the ribociclib + ET group and 89 (3.6%) in the ET only group. Deaths were most often attributed to disease recurrence/disease progression (58 patients; 2.3% vs. 73 patients; 3.0%, respectively). All deaths attributed to AE were observed in 16 patients or 0.6% in the ribociclib + ET group and in 4 patients or 0.2% in the ET only group. All deaths attributed to other reasons (other than disease recurrence/progression or AE) were observed at a similar incidence by group, 9 patients or 0.4% vs. 12 patients or 0.5%; and the primary cause, nature, and timing of these deaths did not yield any pattern [SCS Add. Study O12301C-Section 2.3].

On-treatment deaths: The incidence of death that was on treatment (up to 36 months of treatment plus 30 days of safety follow-up) was 0.8% (ribociclib + ET: 20 patients) vs. 0.4% (ET only: 9 patients). The incidence of on-treatment death attributed to disease recurrence/disease progression was 0.4% (9 patients) vs. 0.2% (4 patients). When the primary reason for on-treatment death was attributed to AE, these presented in 11 patients (0.4%) in the ribociclib + ET group and 4 patients (0.2%) in the ET only group. In the ribociclib + ET group, these included COVID-19, COVID-19 pneumonia (3 patients, each); pulmonary embolism (2 patients); and brain edema, cardiac arrest, road traffic accident (1 patient, each). In the ET only group, these included COVID-19, congestive cardiac failure, MI, and sepsis (1 patient, each). Overall, there is no evidence that the deaths due to COVID-19 events in the ribociclib + ET group were associated with drug-emergent myelosuppression. There was 1 death on-treatment with unknown reason in the ET only group, which was reported as death PT [Study O12301C EA&SU-Section 4.3.3.1] [CO Study O12301-Section 5.2.2].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment, with the clarification that FDA considers it likely that ribociclib contributed to the imbalance in deaths due to COVID-19. Detailed narratives and case report forms were provided by the Applicant for NATALEE participants with on-treatment deaths (on treatment or within 30 days of discontinuation) in either arm and have been reviewed.

On-treatment deaths were infrequent, as expected in an adjuvant trial, but more common in the ribociclib + ET arm than in the ET only arm [20 (0.8%) versus 9 (0.4%)], attributed equally to recurrent/progressive disease and adverse events. Although the ribociclib + ET group continued to have more deaths due to adverse events (0.6% versus 0.2%) at the time of the final iDFS data cut-off, there were fewer overall on-study deaths in the ribociclib + ET arm (3.6% versus 3.3%) due to a relative decrease in recurrences in the ribociclib + ET arm compared to the ET only arm with time.

FDA's analysis of deaths by study period and cause of death is shown in the table below.

Table 24: FDA – Analysis of Deaths by Study Period and Cause of Death

	Ribociclib + ET N = 2525 N (%)	ET only N = 2442 N (%)
Total Deaths	**83 (3.3)**	**89 (3.6)**

	Ribociclib + ET N = 2525 N (%)	ET only N = 2442 N (%)
Disease Recurrence/progression	58 (2.3)	73 (3.0)
Adverse Event	16 (0.6)	4 (0.2)
Other	9 (0.4)	12 (0.5)
Within 30 days after last dose	***25 (1.0)***	***9 (0.4)***
Adverse Event	15 (0.6)	4 (0.2)
Disease Recurrence/progression	10 (0.4)	4 (0.2)
Other	0	1 (<0.1)
Beyond 30 days after last dose	***58 (2.3)***	***80 (3.3)***
Disease Recurrence/progression	48 (1.9)	69 (2.8)
Other	9 (0.4)	11 (0.5)
Adverse Event	1 (<0.1)	0

Source: ADSL (Subject-Level Analysis Dataset) - 2023-12-22. Variables used: USUBJID, TRT01A, SAFFL, DTHCAUSE, DTHDT, DTHFL, TRTEDT

The Applicant's analysis of specific causes of death shown in Table 23 has been replicated by FDA, and case report forms for patients with fatal AEs were reviewed. The most notable pattern identified in the deaths was that were more patients who died of COVID-19 or COVID-19 pneumonia in the ribociclib + ET group (n=6) than in the ET only (n=1) group. Of note, six of the seven total patients who died of COVID-19 or COVID-19 pneumonia (Participant IDs: (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6)) were either known to be unvaccinated or had no vaccination reported. The only vaccinated patient who died of COVID-19 (Participant ID: (b) (6)) was randomized to the ribociclib arm and had received 2 doses of an AstraZeneca vaccine that is not approved for use in the U.S., with no booster shot reported.

Patients on ribociclib were also more likely to be diagnosed with a SARS-CoV-2 (COVID-19) infection. A total of 791 AEs of COVID-19 infections were reported on study, 477 (18.9%) in the ribociclib + ET arm and 314 (12.8%) in the ET only arm. The six deaths on the ribociclib arm from COVID-19 correspond to a case fatality rate of 1.26% compared to 1 death (0.3%) on the ET only arm. Although these are very small numbers, and therefore point estimates should be interpreted with caution, this suggests that patients on ribociclib are more likely to become infected with SARS-CoV-2, and for those who are infected, more likely to have a poor outcome.

These COVID-19 deaths did not appear to be associated with treatment-emergent neutropenia, which is unsurprising given that neutropenia more typically predisposes to bacterial infections than viral. As shown in Table 30, while low lymphocyte counts were very common in both groups on study, the grade of lymphopenia was higher for those receiving ribociclib; 19.1% of patients on the ribociclib + ET arm had grade 3/4 lymphopenia compared to 6.3% of those receiving ET alone. It is possible that this may

have contributed to the increased incidence and severity of COVID-19 infections in patients who received ribociclib.

About half of the NATALEE population was enrolled during the pandemic, many before COVID-19 vaccines and therapeutics were widely available in the regions where the trial was conducted. The protocol did not require vaccination or ascertainment of vaccination status, and thus this information was not available for many participants. No COVID-19 deaths were reported to have occurred in NATALEE after early 2022, which likely reflects a growing level of population immunity from vaccination and/or prior infection, as well as availability of treatments for acute COVID-19 infection.

While these data are reassuring at this time, an increased risk of COVID-19 with ribociclib could be of greater future concern as immunity wanes, especially if SARS-CoV-2 variants with significant immune escape emerge. According to CDC data as of August 3, 2024, only 22.8% of Americans had received the most recent COVID-19 booster shot, and 41.8% stated that they will probably or definitely not get a future COVID-19 booster. It is possible that ribociclib will be associated with more cases of severe or fatal COVID-19 in the postmarketing setting given poor U.S. uptake of COVID-19 boosters, and oncologists should encourage their patients to receive booster shots based upon CDC recommendations for people with cancer. The risk of COVID-19 in patients on ribociclib will continue to be monitored in the postmarket setting, and the USPI will be updated as needed.

Narratives of patients who died of COVID-19 in the investigational arm are below:

Participant ID# (b) (6) is a 71-year-old female with PMH of hypertension, hyperlipidemia, impaired fasting glucose, hypothyroidism, asthma, and obesity. She was diagnosed (b) (6) with Stage IIB breast cancer treated with right lumpectomy, SLNB, breast radiotherapy, and adjuvant chemotherapy with AC-T. She was randomized to ET + ribociclib. Her WBC and ANC were normal at baseline. The patient was vaccinated in (b) (6) and boosted in (b) (6) On Study Day 853, she presented to the ER with fever and abdominal pain and was hypotensive. She was diagnosed with cholelithiasis and was noted to have grade 2 abnormal creatinine, normal WBC and ANC, and was found to have E coli in blood and urine culture. She was hospitalized with a diagnosis of grade 3 pyelonephritis, grade 3 cholecystitis, grade 3 hydronephrosis, grade 3 hypotension, and grade 4 septic shock. All study drugs were interrupted on Study Day 853 and 854 and she received broad spectrum antibiotics and fluids. She tested negative for SARS-CoV-2. She developed grade 4 respiratory failure secondary to septic shock on Study Day 854. She was admitted to the ICU and found to have mild systolic dysfunction with EF of 50%. Blood and urine cultures confirmed E coli. Ultrasound showed gallstones and cholecystitis, and she underwent cholecystostomy drain placement. She was emergently intubated for increased O2 requirement and respiratory distress and on Study Day 855, developed grade 2 atrial fibrillation. On Study Day 856, she had elevated WBC, grade 2 creatinine, grade 1 elevated fasting glucose, and grade 1 GGT. Cultures showed no growth. Atrial fibrillation resolved on Study Day 858, and was moved out of the ICU on Study Day 859. On Study Day 860, she developed dyspnea, fever, and fatigue on Study Day 860 with increasing O2 requirement on Study Day 861 and tested positive for SARS-CoV-2. A CT showed fibrotic lung disease and COPD. She was diagnosed with grade 3 COVID pneumonia and grade 1 pulmonary fibrosis on Study Day 861. She had letrozole restarted on Study Day 863, but ribociclib was

never re-started. Re-intubation was discussed on Study Day 864, but the patient declined. Over the next 10 days, her respiratory status worsened, and on Study Day 874, she died of COVID-19 pneumonia. The Investigator did not suspect a relationship between sepsis, pyelonephritis, cholecystitis, hypotension, hydronephrosis, respiratory failure, and COVID-19 and the study drugs. The patient had multiple risk factors for severe COVID-19 including impaired fasting glucose, obesity, and asthma, as well as older age. She was vaccinated. While she did not have documented neutropenia, it is possible that ribociclib contributed to her death as COVID-19 was nosocomially acquired while admitted for the other AEs.

Participant ID# (b) (6) is a 66-year-old female with PMH of hypertension, diabetes, asthma, autoimmune chronic hepatopathy, and obesity. She was diagnosed with Stage IIB breast cancer on (b) (6), and treated with left mastectomy, ALND, adjuvant EC-T and radiation. At baseline, she had grade 1 leukopenia. No COVID vaccination was reported. In (b) (6) (exact date unknown), she tested positive for SARS-CoV-2, and the patient was diagnosed with COVID-19. She was hospitalized in the intensive care unit with dates of hospitalization not reported per family physician. Concomitant adverse events at the time were rash (grade 1), hypomagnesaemia (grade 1), right hypochondrial pain (abdominal pain upper, grade 1), and scapulohumeral joint pain (arthralgia, grade 2). Her last dose of ribociclib was on Study Day 581, and ribociclib was interrupted due to COVID-19 on Study Day 589 and never restarted. Anastrozole was permanently discontinued on Study Day 593. No treatment was reported for COVID-19, and on Study Day 593, she died of COVID-19. It is unknown if an autopsy was performed. The last ANC available on Study Day 505 was normal, and there was grade 1 leukopenia. The Investigator did not suspect a relationship between COVID-19 and study medicines. FDA considered it possible that ribociclib contributed to her death, although the patient had multiple risk factors for severe COVID-19 including diabetes, obesity, asthma, and older age and no COVID vaccination was reported. The lowest ANC the patient had recorded at any point on study was 1070, and she did not appear to be neutropenic as of the most recent labs available.

Participant ID# (b) (6) is a 64-year-old female patient with PMH of obesity and a prior contralateral left Stage IIB breast cancer. She was diagnosed with Stage IIA breast cancer on (b) (6), and treated with right mastectomy and ALND. She began ribociclib and anastrozole on (b) (6). In (b) (6) (exact date unknown, limited details available), she tested positive for SARs-CoV-2 and was diagnosed with COVID-19 and hospitalized. No COVID-19 vaccination was reported. Concomitant adverse events at the time were grade 1 dermatitis, lacrimation increased, headache, and hot flush. Ribociclib was permanently discontinued on Study Day 833 due to COVID-19, and anastrozole was permanently discontinued due to COVID-19 on Study Day 840. On Study Day 851, she died of COVID-19. No information about concomitant medications, the hospitalization, medications for COVID-19, or any autopsy was available. The Investigator did not suspect a relationship between COVID-19 and the study medications ribociclib and anastrozole. The patient had risk factors for severe COVID-19 including obesity and older age, and no COVID-19 vaccination was reported. FDA considers it possible that ribociclib contributed to her death, although neutropenia was not reported.

Participant ID# (b) (6) is a 64-year-old female with PMH of hypertension, type 2 DM, chronic cardiac failure, and obesity. She was diagnosed with Stage IIIB breast cancer on

(b) (6), and treated with neoadjuvant AC, right mastectomy, ALND, and radiotherapy. No relevant laboratory abnormalities were noted at screening. No COVID-19 vaccination was reported. She began ribociclib and anastrozole. On Study Day 762, she developed fever, cough, and dyspnea. On Study Day 764, she tested positive for SARS-CoV-2, and she was hospitalized with grade 4 COVID-19. No relevant laboratory abnormalities were reported. Ribociclib was interrupted due to COVID-19 on Study Day 757, having last received a dose on Study Day 749, and never restarted. Anastrozole was permanently discontinued due to COVID-19 on Study Day 762. Her condition worsened, and despite mechanical ventilation, on Study Day 765 she died of COVID-19. Autopsy was reportedly performed, but results were unavailable. The Investigator did not suspect a relationship between COVID-19 and the study medications. The patient had multiple risk factors for severe COVID-19 including diabetes, obesity, and chronic heart failure as well as older age, and no prior COVID vaccination was reported. FDA considers it possible that ribociclib contributed to her death, although neutropenia was not reported.

Participant ID# (b) (6) is a 64-year-old female with PMH of hypertension, grade 2 chronic cardiac failure, chronic pancreatitis, obesity, and diffuse changes in liver parenchyma. She was diagnosed with Stage IIB breast cancer on (b) (6), and treated with neoadjuvant chemo with AC, right mastectomy, ALND, radiation, and adjuvant docetaxel. At screening, she had grade 1 leukopenia and neutropenia. She began treatment with ribociclib and anastrozole. She was diagnosed with worsening cardiopulmonary failure to grade 3 in (b) (6) (exact date unknown) and was hospitalized on Study Day 424 with Grade 4 COVID-19 pneumonia after she developed fever and dyspnea and tested positive for SARS-CoV-2 with an x-ray that revealed bilateral pneumonia. Anastrozole and ribociclib were discontinued the same day. She received unspecified medications as well as mechanical ventilation for COVID-19 and died of COVID-19 pneumonia and cardiopulmonary failure on Study Day 440. An autopsy was performed but results were not available. The Investigator did not suspect a relationship between COVID-19 and study drugs. The patient had multiple risk factors for severe COVID-19 including obesity, chronic cardiac failure, and older age. Her vaccination status is unknown. FDA considers it possible that ribociclib contributed to her death, although worsening of neutropenia from baseline was not reported.

Participant ID# (b) (6) is a 49-year-old female with PMH of obesity and autoimmune thyroiditis. She was diagnosed with Stage IIB breast cancer on (b) (6), and treated with neoadjuvant EC-T, left mastectomy, ALND, radiotherapy. No COVID-19 vaccination was reported. Laboratories were normal at baseline. She began treatment with letrozole, goserelin, and ribociclib. On Study Day 169, she developed fever, myalgia, fatigue, diarrhea, headache, cough, and dyspnea and was diagnosed with grade 3 COVID-19 and COVID-19 pneumonia with ARDS. Ribociclib was interrupted on Study Day 169 (last dose on Study Day 161) and not restarted. Goserelin was last given on Study Day 170. On Study Day 170, she had grade 1 neutropenia (ANC 1570) and leukopenia (WBC 3280). On Study Day 173, she tested positive for SARS-CoV-2. Letrozole was interrupted on Study Day 174 and not restarted. She was hospitalized on Study Day 178 due to COVID-19 pneumonia and treated with steroids, ipratropium, oxygen, and mechanical ventilation. On Study Day 183, she died of COVID-19 pneumonia. The Investigator did not suspect a relationship between COVID-19 and study drugs. The patient had several risk factors for severe

COVID-19 including obesity and autoimmune disease with no prior COVID-19 vaccination reported. FDA considers it possible that ribociclib contributed to her death, although neutropenia and leukopenia were grade 1.

Other causes of death due to AE included pulmonary emboli, which were reported in two patients (0.1%) on the ribociclib + ET arm and none on the ET only arm.

Participant ID: (b) (6) was a 66-year-old postmenopausal female with PMH of diabetes, hypertension, obesity, and lumbar discopathy. She had right-sided pathological stage IIB breast cancer diagnosed on (b) (6), and treated with mastectomy, axillary lymph node dissection (ALND), postmastectomy radiation, adjuvant AC-docetaxel, and adjuvant tamoxifen. She began study treatment with ribociclib and letrozole on (b) (6). She was hospitalized on study day #356 for back pain with no further information and again from study day #377-389 for back pain with an L3 spinal compression fracture without associated bone metastasis. One day later, she was hospitalized for a third time on study day #390 for the same reason and underwent surgery on L3 vertebral body on study day #391 followed by discharge on study day #393. She was readmitted with dyspnea on study day #399 and was diagnosed with a pulmonary embolism, which was fatal. The investigator did not suspect a relationship between the PE and study drugs and attributed the PE to the recent orthopedic surgery. FDA considers the contribution of ribociclib to pulmonary embolism possible, but notes that orthopedic surgery is high risk for thromboembolic events, especially in older adults, and considers this the more likely explanation given the timing of the event.

Participant ID# (b) (6) is a 73-year-old female with PMH of hypertension. She was diagnosed with Stage IIIC breast cancer on (b) (6), and treated with right lumpectomy, ALND, adjuvant chemotherapy with EC-T, radiotherapy, and began letrozole and ribociclib. She had a dose reduction to 200 mg daily on Study Day 169 for reason of patient request. She had grade 3 back pain reported on Study Day 776 treated with peri-radicular therapy. She had grade 3 hypertensive crisis on Study Day 788 that was considered ongoing for which she had been prescribed candesartan. On Study Day 797, she died suddenly at home due to suspected pulmonary embolism. Concomitant AEs at the time death was reported included grade 3 hypertensive crisis, grade 3 back pain, grade 2 nausea, dizziness, knee pain, and grade 1 alopecia, arthralgia, and fatigue. There was no reported diagnostic or lab assessment and no treatment for suspected PE. No autopsy was performed. Ribociclib and letrozole were presumed to be ongoing until the day of death. The Investigator suspected a relationship between letrozole, but not ribociclib, and suspected pulmonary embolism. Though the diagnosis of suspected pulmonary embolism was not confirmed, and available diagnostic information is limited, the Agency considers the death from suspected pulmonary embolism to have been possibly related to study drug in the absence of an alternative explanation.

One patient (<0.1%) on the ribociclib + ET arm died of brain edema and epilepsy compared to none on the ET only arm. Participant ID#: (b) (6) was a 32-year-old premenopausal female with no relevant past medical history who was diagnosed with right-sided pathological stage IIIC breast cancer on (b) (6), and treated with neoadjuvant AC-T, breast conserving surgery and ALND with radiation to the breast and regional nodes. She was noted to have QTcF of 426 ms at baseline. On Study Day #80, she developed

grade 3 diplopia, dizziness, dysarthria, and syncope. A brain MRI did not show an acute CVA. The patient underwent a comprehensive neurologic examination, and she was hospitalized with the diagnosis of grade 3 asthenic-neurotic syndrome ("personality disorder"). On Study Day 81, an ECG was performed, and the results were considered clinically insignificant. Concomitant adverse events at the time were grade 1 headache, neck pain, and neuritis. Concomitant medications at the time of event onset included Calcium D3 (calcium carbonate and colecalciferol) for hypocalcaemia; glycine, bendazol, and citicoline for neuritis; and methylethylpiridinol succinate for peripheral neuropathy. The last dose of ribociclib had been taken on Study Day 77, and ribociclib was interrupted due to syncope, diplopia, dizziness, and dysarthria from Study Day 86 and never restarted. No action was taken with either anastrozole or goserelin due to any of these events. The patient was treated with amitriptyline, thioctic acid, and glycine for syncope and amitriptyline, diphenhydramine, procaine, magnesium sulfate, and metamizole sodium monohydrate for "personality disorder." No treatment was reported for diplopia, dizziness, and dysarthria. On Study Day 89, the patient tested positive for SAR-CoV-2, and she was diagnosed with grade 2 COVID-19. No action was taken with the anastrozole and goserelin due to COVID-19. She was treated with favipiravir, dexamethasone, interferon alfa-2B, tizanidine, and enoxaparin for asymptomatic COVID-19. Dizziness, dysarthria, diplopia, and syncope were improving. On Study Day 98, asymptomatic COVID-19 resolved, and she was discharged from the hospital. On Study Day 190, she was hospitalized again due to "personality disorder." On Study Day 210, she was diagnosed with severe epilepsy and severe cerebral edema and died the same day of these conditions. Details regarding treatments for epilepsy and brain edema were not reported. Autopsy performed on (b) (6) confirmed brain edema and epilepsy as the primary causes of patient´s death. Personality disorder, syncope, diplopia, dizziness, and dysarthria were reported to be ongoing at the time of death. The clinical picture is confounded by COVID-19, which is now well-known to cause neurological complications, especially in hospitalized patients; however, given the concurrent dysarthria, diplopia, and syncope, and subsequent seizure and cerebral edema, FDA believes this patient was most likely misdiagnosed as having a personality disorder by physicians who failed to recognize and treat her underlying and ultimately fatal neurological condition. The contribution of ribociclib to these events is uncertain.

Other causes of on-treatment death due to AE include cardiac arrest, which was reported on treatment in one patient (<0.1%) on the ribociclib + ET arm and none on the ET only arm. Though not known to have been associated with QT prolongation, this patient narrative is discussed below in Section 8.2.5.2 on the QT prolongation AESI.

Serious Adverse Events

Data:

Table 25: Serious adverse events by preferred term and worst toxicity grade, irrespective of causality, with incidence at least 0.2% / either group in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 cut-off							
	Ribociclib + ET N=2525				ET only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
No. pts with at least 1 AE	357 (14.1)	252 (10.0)	44 (1.7)	11 (0.4)	256 (10.5)	192 (7.9)	26 (1.1)	4 (0.2)
COVID-19	20 (0.8)	13 (0.5)	0	3 (0.1)	13 (0.5)	9 (0.4)	0	1 (< 0.1)
Pneumonia	14 (0.6)	12 (0.5)	0	0	9 (0.4)	7 (0.3)	0	0
Pulmonary embolism	15 (0.6)	11 (0.4)	1 (< 0.1)	2 (0.1)	5 (0.2)	5 (0.2)	0	0
Dyspnoea	12 (0.5)	9 (0.4)	0	0	5 (0.2)	3 (0.1)	0	0
Alanine aminotransferase increased	9 (0.4)	1 (< 0.1)	7 (0.3)	0	0	0	0	0
Breast cellulitis	9 (0.4)	9 (0.4)	0	0	3 (0.1)	3 (0.1)	0	0
COVID-19 pneumonia	9 (0.4)	5 (0.2)	0	3 (0.1)	5 (0.2)	4 (0.2)	1 (< 0.1)	0
Humerus fracture	8 (0.3)	7 (0.3)	0	0	4 (0.2)	3 (0.1)	0	0
Cellulitis	7 (0.3)	7 (0.3)	0	0	6 (0.2)	6 (0.2)	0	0
Cholelithiasis	7 (0.3)	6 (0.2)	1 (< 0.1)	0	5 (0.2)	5 (0.2)	0	0
Pyrexia	7 (0.3)	2 (0.1)	0	0	1 (< 0.1)	1 (< 0.1)	0	0
Atrial fibrillation	7 (0.3)	5 (0.2)	1 (< 0.1)	0	8 (0.3)	7 (0.3)	0	0
Drug-induced liver injury	6 (0.2)	2 (0.1)	3 (0.1)	0	0	0	0	0
Urinary tract infection	6 (0.2)	6 (0.2)	0	0	3 (0.1)	3 (0.1)	0	0
Aspartate aminotransferase increased	5 (0.2)	2 (0.1)	3 (0.1)	0	0	0	0	0
Diarrhoea	5 (0.2)	3 (0.1)	0	0	0	0	0	0
Hepatotoxicity	5 (0.2)	3 (0.1)	2 (0.1)	0	0	0	0	0
Papillary thyroid cancer	5 (0.2)	5 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Postoperative wound infection	5 (0.2)	5 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Appendicitis	4 (0.2)	3 (0.1)	1 (< 0.1)	0	2 (0.1)	2 (0. 1)	0	0
Cerebrovascular accident	5 (0.2)	2 (0.1)	0	0	1 (< 0.1)	0	1 (< 0.1)	0
Acute myocardial infarction	4 (0.2)	1 (< 0.1)	3 (0.1)	0	0	0	0	0
Mastitis	4 (0.2)	2 (0.1)	0	0	2 (0.1)	2 (0.1)	0	0
Osteoarthritis	4 (0.2)	4 (0.2)	0	0	4 (0.2)	4 (0.2)	0	0
Pneumonia viral	4 (0.2)	0	0	0	3 (0.1)	1 (< 0.1)	0	0
Suspected COVID-19	4 (0.2)	0	0	0	1 (< 0.1)	0	0	0
Syncope	4 (0.2)	4 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0

	Final iDFS analysis: 21-Jul-2023 cut-off							
	Ribociclib + ET N=2525				ET only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Erysipelas	4 (0.2)	2 (0.1)	0	0	3 (0.1)	2 (0.1)	0	0

Source: [SCS Add. Study O12301C-Table 2-8]

The Applicant's Position:

Incidence of SAEs was 14.1% in the ribociclib + ET group vs. 10.5% in the ET only group. The most frequently reported SAEs by PT (in at least 10 patients) in the ribociclib + ET group were COVID-19 (0.8%), pneumonia (0.6%), pulmonary embolism (0.6%), and dyspnea (0.5%). COVID-19 (0.5%) was the only SAEs reported in 10 or more patients in the ET only group. Considering the low rates of individual PTs, no pattern in the reported SAEs was identified in either treatment group [CO Study O12301-Section 5.2.2].

The FDA's Assessment:

Detailed narratives and case report forms for NATALEE participants with grade ≥3 SAEs on the ribociclib plus endocrine therapy arm have been reviewed, and the incidence of SAEs has been verified by FDA. FDA generally agrees with the Applicant's assessment of SAEs. SAEs occurred in 14% of patients on ribociclib + ET compared to 10% on ET only. Most SAEs were grade 3. Grade ≥4 SAEs occurred in 2.1% of participants randomized to receive ribociclib versus 1.3% of the control group.

As reflected in the USPI and discussed in further detail in Section 8.2.5.3 under hepatobiliary AESIs, hepatic SAEs (increased AST or ALT, hepatotoxicity, or drug-induced liver injury) were among the most common SAEs and occurred exclusively in patients who received ribociclib. These were also the most common grade 4 SAEs.

Given the very high incidence of neutropenia with ribociclib and the prolonged exposure to ribociclib in the adjuvant setting, infections were expected to be among the most common SAEs in NATALEE. As discussed in Section 8.2.5.1 on the neutropenia AESI, the risk of serious infections was low in both arms, but there was a consistent slight increase in infectious SAEs with the addition of ribociclib to endocrine therapy compared to endocrine therapy alone. The majority of these were respiratory or cutaneous.

COVID-19 and COVID-19 pneumonia, including fatal cases, were more common in patients on the ribociclib + ET arm. COVID-19 has been discussed in further detail above in Section 8.2.4 on on-treatment deaths. In addition to these confirmed cases of COVID-19 and COVID-19 pneumonia, there were additional SAEs that suggested a small increase in risk of SAEs due to potentially undiagnosed COVID-19 or other respiratory infections, including pneumonia (0.6% vs 0.4%), viral pneumonia (0.2% vs 0.1%), and suspected COVID-19 (0.2% vs <0.1%). The incidence of oral herpes was also noted to be increased (1.5% vs 0.5%). As described above, grade 3/4 lymphopenia was more common in patients receiving ribociclib in combination with ET (19.1% vs 6.3%) and may have contributed to an increased risk of viral infection.

Most of the remaining infectious SAEs were local/cutaneous infections. While rare overall, these local/cutaneous infections including breast cellulitis (0.4% vs 0.1%), mastitis (0.2% vs 0.1%), postoperative wound infection (0.2% versus 0.1%), and erysipelas (0.2% vs 0.1%) were similarly slightly more common in patients who received ribociclib.

An FDA analysis of thrombosis overall as a grouped term found an approximate doubling of the incidence of all-grade AEs with ribociclib + ET (1.7%) compared to ET alone (0.9%). Most of these AEs were grade 1-2 in severity, but the incidence of the rare, more severe, AEs related to thrombosis was similarly doubled: 15 patients (0.6%) had a grade ≥ 3 thrombosis AE on the ribociclib + ET arm compared with 8 (0.3%) on ET alone. This includes one patient with grade 4 AE and 2 patients with fatal thrombosis-related AEs on the ribociclib + ET arm compared with none on the ET only arm. Thromboembolic SAEs including pulmonary emboli (0.6% vs 0.2%), myocardial infarction (0.2% vs 0.1%), and cerebrovascular accidents (0.2% vs 0%) were also reported slightly more commonly in the ribociclib + ET only group. Narratives for the two patients with grade 5 AEs, both pulmonary emboli, on the ribociclib + ET arm are discussed in further detail above in Section 8.2.4.

These hepatic and thromboembolic SAEs may be observed more commonly in the postmarketing setting as patients who would have been excluded from NATALEE due to comorbid conditions are treated with ribociclib for early breast cancer. Adverse events in these system organ classes will continue to be monitored in the postmarket setting and the ribociclib USPI updated for safety as appropriate.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 26: Adverse events leading to discontinuation by preferred term and worst toxicity grade, irrespective of causality, with at least 0.2% / either group in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 data cut-off							
	Ribociclib + ET N=2525				**ET only N=2442**			
Preferred term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
No. pts with at least 1 AE	524 (20.8)	201 (8.0)	36 (1.4)	2 (0.1)	134 (5.5)	38 (1.6)	5 (0.2)	3 (0.1)
Alanine aminotransferase increased	180 (7.1)	84 (3.3)	19 (0.8)	0	2 (0.1)	1 (< 0.1)	0	0
Aspartate aminotransferase increased	71 (2.8)	28 (1.1)	7 (0.3)	0	0	0	0	0
Arthralgia	37 (1.5)	4 (0.2)	0	0	49 (2.0)	9 (0.4)	0	0
Fatigue	18 (0.7)	3 (0.1)	0	0	1 (< 0.1)	0	0	0
Neutropenia	19 (0.8)	15 (0.6)	2 (0.1)	0	0	0	0	0

	Final iDFS analysis: 21-Jul-2023 data cut-off							
	Ribociclib + ET N=2525				ET only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Neutrophil count decreased	7 (0.3)	7 (0.3)	0	0	0	0	0	0
Nausea	13 (0.5)	1 (< 0.1)	0	0	1 (< 0.1)	0	0	0
Hepatotoxicity	7 (0.3)	4 (0.2)	2 (0.1)	0	0	0	0	0
Rash	7 (0.3)	2 (0.1)	0	0	2 (0.1)	0	0	0
Asthenia	11 (0.4)	5 (0.2)	0	0	0	0	0	0
Blood magnesium decreased	7 (0.3)	0	0	0	0	0	0	0
Headache	7 (0.3)	1 (< 0.1)	0	0	3 (0.1)	0	0	0
Blood creatinine increased	8 (0.3)	1 (< 0.1)	0	0	0	0	0	0
COVID-19	8 (0.3)	2 (0.1)	2 (0.1)	1 (< 0.1)	1 (< 0.1)	0	1 (< 0.1)	0
Diarrhoea	7 (0.3)	2 (0.1)	0	0	2 (0.1)	0	0	0
Electrocardiogram QT prolonged	7 (0.3)	2 (0.1)	0	0	0	0	0	0
Hypomagnesaemia	6 (0.2)	0	0	0	0	0	0	0
Alopecia	5 (0.2)	0	0	0	0	0	0	0
Pneumonitis	5 (0.2)	0	0	0	0	0	0	0
Pulmonary embolism	4 (0.2)	3 (0.1)	1 (< 0.1)	0	1 (< 0.1)	1 (< 0.1)	0	0
Anxiety	4 (0.2)	1 (< 0.1)	0	0	1 (< 0.1)	0	0	0
Hyperkalaemia	4 (0.2)	1 (< 0.1)	0	0	0	0	0	0
Hypertransaminasaemia	4 (0.2)	1 (< 0.1)	0	0	0	0	0	0
Papillary thyroid cancer	4 (0.2)	4 (0.2)	0	0	0	0	0	0
Gamma-glutamyltransferase increased	3 (0.1)	2 (0.1)	0	0	0	0	0	0
Hypercalcaemia	5 (0.2)	0	0	0	0	0	0	0
Myalgia	2 (0.1)	1 (< 0.1)	0	0	5 (0.2)	2 (0.1)	0	0

Source: [SCS Add. Study O12301C-Table 2-9]

The Applicant's Position:

Overall, AEs leading to discontinuation of study treatment were observed at a higher frequency (relative difference between treatment groups) in the ribociclib + ET group (20.8%) vs. the ET only group (5.5%) [SCS Add. Study O12301C-Table 2-9]. The discontinuation rate was relatively low for each individual event, indicating these events were manageable. The median

relative dose intensity (RDI) for ribociclib was 94.0% (range: 14 to 132), and the median RDI for NSAI in both the ribociclib + ET and ET only groups was 100%, indicating the addition of ribociclib continued to not affect the tolerability of NSAI/ET.

The most frequently reported AEs (in ≥ 10 patients) leading to study treatment drug discontinuation in the ribociclib group plus ET group were increased ALT (7.1%), increased AST (2.8%), arthralgia (1.5%), neutropenia (0.8%), fatigue (0.7%), and nausea (0.5%,). The most frequent AE leading to study treatment discontinuation in the ET only group was arthralgia (2.0%). Overall, the proportion of grade-3 and grade-4 AEs leading to discontinuation continued to be higher with ribociclib + ET (8.0% and 1.4%, respectively) vs. ET only (1.6% and 0.2%, respectively). When required, most ribociclib discontinuations occurred early during study treatment, with a median of approximately 4 months [CO Study O12301-Section 5.2.2].

The FDA's Assessment:

FDA has analyzed AEs leading to discontinuation of study drug and generally agrees with the Applicant's assessment. As discussed earlier, the toxicities of ribociclib and ET are largely non-overlapping, and co-administration of ribociclib with ET had a limited effect on the delivery of standard adjuvant ET.

Adverse events leading to treatment discontinuation were increased almost fourfold with the addition of ribociclib to ET (20.8% vs 5.5%). The most common AEs that led to discontinuation in the ribociclib group were increased transaminases, which most commonly occur in the first two to three months of treatment and are a known AESI with ribociclib for which there is an existing warning in the USPI. Hepatotoxicity as an AESI associated with ribociclib is discussed in further detail in Section 8.2.5.3.

While neutropenia is also common and tended to occur early in treatment, it was well-managed with treatment interruption or dose reduction, as discussed below, and required ribociclib discontinuation in <1% of patients. As noted in the section above on SAEs, serious infections were uncommon and predominantly respiratory or cutaneous. Neutropenia as an AESI is discussed in further detail in Section 8.2.5.1. The only on-study deaths due to infections in the ribociclib + ET arm were COVID-19 or COVID-19 pneumonia and not associated with treatment-emergent neutropenia. These deaths are reviewed in further detail above in Section 8.2.4.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 27: Adverse events leading to study drug interruption by preferred term and worst toxicity grade, irrespective of causality, with incidence at least 2% / either group in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 cut-off							
	Ribociclib + ET N=2525				ET Only N=2442			
Preferred Term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
No. pts with at least 1 AE	1858 (73.6)	1226 (48.6)	87 (3.4)	0	199 (8.1)	67 (2.7)	8 (0.3)	0

	Final iDFS analysis: 21-Jul-2023 cut-off							
	Ribociclib + ET N=2525				ET Only N=2442			
Preferred Term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Neutropenia	683 (27.0)	637 (25.2)	30 (1.2)	0	1 (< 0.1)	0	1 (< 0.1)	0
Neutrophil count decreased	441 (17.5)	411 (16.3)	17 (0.7)	0	2 (0.1)	1 (< 0.1)	1 (< 0.1)	0
Alanine aminotransferase increased	255 (10.1)	116 (4.6)	16 (0.6)	0	7 (0.3)	2 (0.1)	1 (< 0.1)	0
COVID-19	228 (9.0)	8 (0.3)	2 (0.1)	0	20 (0.8)	3 (0.1)	0	0
Aspartate aminotransferase increased	171 (6.8)	56 (2.2)	8 (0.3)	0	7 (0.3)	4 (0.2)	0	0
Hypomagnesaemia	127 (5.0)	0	1 (< 0.1)	0	0	0	0	0
SARS-CoV-2 test positive	115 (4.6)	0	0	0	8 (0.3)	0	0	0
Leukopenia	81 (3.2)	45 (1.8)	0	0	0	0	0	0
Hyperkalaemia	81 (3.2)	3 (0.1)	0	0	0	0	0	0
Hypocalcaemia	81 (3.2)	1 (< 0.1)	0	0	0	0	0	0
Hypokalaemia	70 (2.8)	4 (0.2)	0	0	0	0	0	0
White blood cell count decreased	70 (2.8)	43 (1.7)	1 (< 0.1)	0	0	0	0	0
Blood magnesium decreased	63 (2.5)	1 (< 0.1)	0	0	0	0	0	0
Pyrexia	73 (2.9)	3 (0.1)	0	0	8 (0.3)	0	0	0
Arthralgia	42 (1.7)	6 (0.2)	0	0	54 (2.2)	15 (0.6)	0	0

Source: [SCS Add. Study O12301C-Table 2-10]

Table 28: Adverse events leading to study drug dose reduction by preferred term and worst toxicity grade, irrespective of causality with incidence at least 0.2% / either group in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 data cut-off							
	Ribociclib + ET N=2525				ET Only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
No. pts with at least 1 AE	586 (23.2)	338 (13.4)	36 (1.4)	0	0	0	0	0
Neutropenia	215 (8.5)	157 (6.2)	23 (0.9)	0	0	0	0	0

	Final iDFS analysis: 21-Jul-2023 data cut-off							
	Ribociclib + ET N=2525				ET Only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Neutrophil count decreased	141 (5.6)	114 (4.5)	13 (0.5)	0	0	0	0	0
Alanine aminotransferase increased	49 (1.9)	21 (0.8)	0	0	0	0	0	0
Fatigue	26 (1.0)	4 (0.2)	0	0	0	0	0	0
White blood cell count decreased	26 (1.0)	6 (0.2)	0	0	0	0	0	0
Leukopenia	17 (0.7)	7 (0.3)	0	0	0	0	0	0
Aspartate aminotransferase increased	16 (0.6)	3 (0.1)	0	0	0	0	0	0
Nausea	11 (0.4)	2 (0.1)	0	0	0	0	0	0
Asthenia	10 (0.4)	2 (0.1)	0	0	0	0	0	0
Alopecia	6 (0.2)	0	0	0	0	0	0	0
Rash	6 (0.2)	1 (< 0.1)	0	0	0	0	0	0
Gamma-glutamyltransferase increased	5 (0.2)	2 (0.1)	0	0	0	0	0	0
Stomatitis	4 (0.2)	0	0	0	0	0	0	0
Diarrhoea	4 (0.2)	2 (0.1)	0	0	0	0	0	0
Headache	4 (0.2)	3 (0.1)	0	0	0	0	0	0
Arthralgia	4 (0.2)	0	0	0	0	0	0	0

Source: [SCS Add. Study O12301C Table 2-11]

The Applicant's Position:

AEs leading to study treatment interruption were observed more frequently in the ribociclib + ET group compared to the ET only group (73.6% vs 8.1%, respectively). Despite the higher frequency of AEs leading to dose interruptions in the ribociclib + ET group, the discontinuation rate was relatively low for each individual event, indicating these events were manageable. In addition, the median RDI of ribociclib was 94.0%, and importantly there was no impact on the ET dose maintenance, which is supported by RDI of 100% for ET in both treatment arms. The most frequent AEs (overall: ≥ 10%) leading to interruption with ribociclib + ET were neutropenia (all grades: 27.0% vs. < 0.1%), followed by neutrophil count decreased (17.5% vs. 0.1%) and increased ALT (10.1% vs. 0.3%) [SCS Add. Study O12301C-Table 2-10]. All remaining AEs leading to study drug interruption were < 10%. The most frequent grade 3/4 AEs leading to study drug interruption in the ribociclib + ET group were also neutropenia and neutrophil count decreased [SCS Add. Study O12301C-Table 2-1 0].

The most frequently reported AEs (with incidences ≥ 2%) that required dose reduction in the ribociclib + ET group were neutropenia (8.5%) and neutrophil count decreased (5.6%). The most frequently reported grade 3 and grade 4 AEs that required ribociclib dose reduction were

neutropenia (grade 3: 6.2%; grade 4: 0.9%) and neutrophil count decreased (grade 3: 4.5%; grade 4: 0.5%) [SCS Add. Study O12301C-Table 2-11].

Neutropenia AEs (PT) leading to dose interruption were frequent in the ribociclib + ET group (27.0%), but the corresponding frequency of neutropenia AEs (PT) leading to discontinuation was only 0.8%.

Importantly, the majority of AEs were effectively resolved with ribociclib dose interruptions and/or reductions [CO Study O12301C-Section 5.2.2].

The FDA's Assessment:

FDA has analyzed AEs leading to study drug interruption and dose reductions and generally agrees with the Applicant's assessment.

Approximately three-quarters of patients on the ribociclib + ET arm required temporary treatment interruption due to an adverse event, most of which were abnormal laboratory values. This is markedly increased over the ET only arm where only 8% of patients required treatment interruption. Combining laboratory abnormalities of neutrophil counts decreased and reported AEs of neutropenia, neutropenia accounted for the majority of ribociclib interruptions/dose reductions. Neutropenia tended to occur in the first few cycles of treatment and was effectively managed for most patients via interruption. About one in seven participants on ribociclib required a dose reduction to 200 mg/day due to grade 3/4 neutropenia. Both permanent discontinuation due to neutropenia (<1%) and clinical complications of neutropenia were rare and are discussed in further detail below. As noted above, while both infections of all grades, as well as SAEs related to infections, were more common in participants receiving ribociclib + ET, infections other than SARS-CoV-2 occurred rarely overall in NATALEE.

In addition to myelosuppression, the other common causes of study drug interruption were also mostly laboratory-related: elevated ALT or AST, SARS-CoV2 test positive or COVID-19, and electrolyte abnormalities (increased or decreased potassium, calcium, or magnesium). A small number of patients also had treatment interruption due to fatigue, arthralgia, and pyrexia.

Ribociclib dose reductions were required in almost 1 in 4 participants on the ribociclib + ET arm and occurred for similar reasons to treatment interruption. More than half of the dose reductions were due to neutropenia/neutrophil count decreased. Other than myelosuppression, the next most common reason for dose reductions was abnormal liver function tests (ALT, AST, or GGT), which resulted in ribociclib discontinuation in approximately 3% of patients. The remaining causes of dose reduction occurred in ≤1% of patients on the ribociclib + ET arm with constitutional symptoms (fatigue, asthenia) and GI symptoms (stomatitis, nausea, and diarrhea) being most common.

Significant Adverse Events

The Applicant's Position:

The significant AEs reported are described in other sections of this document, "Serious Adverse Events" and "Treatment Emergent Adverse events and Adverse Reactions".

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment with the addition of the concern regarding an increased incidence of severe/fatal COVID-19 and COVID-19 pneumonia. This appears to have been mitigated later in the trial with availability of COVID-19 vaccination and therapeutics, as well as likely immunity related to prior infections. This risk is discussed in further detail earlier in Section 8.2.4 in the section about on-treatment deaths.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 29: Common adverse events with grade ≥ 3 events at incidence ≥ 1.0% in either group, by preferred term in Study O12301C (Safety set)

	Final iDFS Analysis (21-Jul-2023 data cut-off)			
	Ribociclib + ET N=2525	only N=2442	Ribociclib + ET N=2525	only N=2442
AE	All grades n (%)	All grades n (%)	Grade ≥ 3 n (%)	Grade ≥ 3 n (%)
Total no. patients with at least 1 TEAE	**2474 (98.0)**	**2145 (87.8)**	**1607 (63.6)**	**469 (19.2)**
Neutropenia	1047 (41.5)	73 (3.0)	707 (28.0)	14 (0.6)
Neutrophil count decreased	609 (24.1)	41 (1.7)	448 (17.7)	8 (0.3)
Alanine aminotransferase increased	492 (19.5)	136 (5.6)	192 (7.6)	17 (0.7)
Aspartate aminotransferase increased	426 (16.9)	139 (5.7)	118 (4.7)	13 (0.5)
White blood cell count decreased	246 (9.7)	38 (1.6)	94 (3.7)	6 (0.2)
Leukopenia	337 (13.3)	50 (2.0)	94 (3.7)	2 (0.1)
Hypertension	212 (8.4)	185 (7.6)	54 (2.1)	59 (2.4)
Gamma-glutamyltransferase increased	119 (4.7)	67 (2.7)	26 (1.0)	22 (0.9)
Lipase increased	58 (2.3)	33 (1.4)	25 (1.0)	12 (0.5)
Arthralgia	942 (37.3)	1058 (43.3)	25 (1.0)	31 (1.3)

Grade ≥ 3 AEs are sorted by decreasing order of frequency in the ribociclib + ET column.

Source: [CO Study O12301C-Table 5-1]

The Applicant's Position:

Most frequent AEs by Preferred term

Overall, AEs were observed at a higher frequency (relative difference between treatment groups) in the ribociclib + ET group vs. ET only group of +10.2%.

AEs observed at a higher frequency (with a ≥ 10% relative difference between treatment groups in overall decreasing order of frequency with ribociclib + ET) included: neutropenia (+38.5%), decreased neutrophil count (+22.4%), nausea (+15.5%), increased ALT (+13.9%), leukopenia (+11.3%), alopecia (+10.5%), and increased AST (+11.2%). In the ET only group, no PT met this criterion. Arthralgia was reported in a greater proportion (6% relative difference) of ET only-treated patients, compared with ribociclib + ET-treated patients [SCS Add. Study O12301C-Section 2.2.2].

Severity of AEs

The majority of the most frequent (≥ 1.0%/either group) grade ≥ 3 AEs were consistent with the known safety profile of ribociclib, predominantly pertaining to the known risk of myelosuppression, occurring usually within the first few cycles of therapy, and the incidence did

not increase over time. The clinical impact of grade ≥ 3 TEAEs on patients in the ribociclib + ET group was limited, as the majority of events were asymptomatic laboratory abnormalities and completely resolved with appropriate management as per protocol [CO Study O12301C CO-Section 5.2.1.2]

Adverse drug reactions

The screening, methodology, and selection process used to identify ADRs for the target population are described in [SCS Study O12301C-Section 1.1.3.5] and [SCS Study O12301C-Appendix 2]. No new ADRs were identified based on the Novartis comprehensive medical evaluation of data from Study O12301C. In addition, the ribociclib ADR profile in patients with HR-positive, HER2-negative eBC is compared favorably with the established safety profile of Kisqali in patients with aBC [SCS Study O12301C-Section 2.9], (Kisqali USPI 2022, Kisqali SmPC 2023). This is due to a considerable number of pre-existing ADRs that did not qualify as ADRs in the eBC setting and several pre-existing ADRs that were downgraded in their frequency category for this patient population. For further details, see [SCS Study O12301C-Section 2.9]. These data are considered robust based on the adequate overall sample size of Study O12301C (N=4968; Safety set) and study design, including the control arm [CO Study O12301-Section 5.5].

No new ADRs or changes in the frequency categories of ADRs identified based on the primary analysis were identified in the target population based on the Novartis comprehensive medical evaluation of data from Study O12301C for the final iDFS analysis.

The FDA's Assessment:

FDA's analysis of common and grade 3/4 AEs generally agrees with the Applicant's analysis/assessment except regarding COVID-19. As SARS-CoV-2 did not yet exist at the time the ribociclib trials were conducted in the metastatic setting, COVID-19 represents a new ADR. The incidence of SARS-CoV-2 infection and COVID-19 illness, including severe or fatal cases, was increased in patients who received ribociclib, as discussed above in Section 8.2.4. Addition of a Warning and Precaution related to COVID-19 was discussed by the review team, but given that the risk of severe illness appears to have diminished over the course of the trial, likely due to the availability of vaccines and COVID-19 therapeutics, as well as immunity related to prior infection, it was not added. If an increase in severe or fatal COVID-19 is observed in the postmarket setting, the USPI will be updated accordingly.

As discussed above and in Section 8.2.5, the most common overall and grade ≥3 treatment-emergent AEs were laboratory findings, in particular myelosuppression and liver function abnormalities, most of which were asymptomatic.

Laboratory Findings

Data:

Table 30: New or worsening postbaseline hematology and clinical chemistry abnormalities, with incidence at least 10% / either group in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 data cut-off					
	Ribociclib + ET N=2525			ET only N=2442		
Safety endpoint (hyper / hypo grade)	**Grade 1/2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Hematology abnormalities						
Hemoglobin (hypo)	1178 (46.7)	14 (0.6)	0	619 (25.3)	8 (0.3)	0
Leukocytes (hypo)	1714 (67.9)	688 (27.2)	5 (0.2)	1089 (44.6)	12 (0.5)	2 (0.1)
Lymphocytes (hypo)	1980 (78.4)	413 (16.4)	67 (2.7)	1998 (81.8)	98 (4.0)	55 (2.3)
Neutrophils (hypo)	1225 (48.5)	1083 (42.9)	55 (2.2)	818 (33.5)	35 (1.4)	6 (0.2)
Platelets (hypo)	705 (27.9)	9 (0.4)	1 (< 0.1)	312 (12.8)	7 (0.3)	1 (< 0.1)
Clinical chemistry abnormalities						
ALT (hyper)	926 (36.7)	167 (6.6)	38 (1.5)	837 (34.3)	24 (1.0)	1 (< 0.1)
ALP (hyper)	884 (35.0)	5 (0.2)	0	884 (36.2)	5 (0.2)	0
Amylase (hyper)	363 (14.4)	24 (1.0)	8 (0.3)	328 (13.4)	29 (1.2)	4 (0.2)
AST (hyper)	978 (38.7)	113 (4.5)	20 (0.8)	780 (31.9)	26 (1.1)	0
Calcium corrected (hyper)	247 (9.8)	5 (0.2)	3 (0.1)	356 (14.6)	9 (0.4)	6 (0.2)
Calcium corrected (hypo)	517 (20.5)	6 (0.2)	16 (0.6)	386 (15.8)	9 (0.4)	29 (1.2)
Creatinine (hyper)	815 (32.3)	7 (0.3)	0	278 (11.4)	0	0
Direct bilirubin (hyper)	456 (18.1)	26 (1.0)	8 (0.3)	426 (17.4)	14 (0.6)	1 (< 0.1)
GGT (hyper)	865 (34.3)	90 (3.6)	8 (0.3)	760 (31.1)	83 (3.4)	6 (0.2)
Glucose (hyper)	1478 (58.5)	48 (1.9)	12 (0.5)	1396 (57.2)	36 (1.5)	12 (0.5)
Lipase (hyper)	407 (16.1)	67 (2.7)	12 (0.5)	400 (16.4)	69 (2.8)	9 (0.4)
Magnesium (hypo)	379 (15.0)	4 (0.2)	3 (0.1)	371 (15.2)	0	1 (< 0.1)
Potassium (hyper)	355 (14.1)	16 (0.6)	1 (< 0.1)	378 (15.5)	15 (0.6)	4 (0.2)
Potassium (hypo)	261 (10.3)	16 (0.6)	7 (0.3)	208 (8.5)	22 (0.9)	14 (0.6)
Sodium (hyper)	276 (10.9)	3 (0.1)	1 (< 0.1)	291 (11.9)	2 (0.1)	0
Sodium (hypo)	270 (10.7)	26 (1.0)	6 (0.2)	230 (9.4)	17 (0.7)	7 (0.3)
Urate (hyper)	771 (30.5)	0	38 (1.5)	701 (28.7)	0	43 (1.8)

Source: [SCS Add. Study O12301C-Table 3-1 and 3-2]

The Applicant's Position:

Most hematology abnormalities were of low-grade, with the exception of neutrophil counts. The most common worst-post-baseline grade 1 / 2 hematological abnormalities in the ribociclib + ET group (≥ 10.0% difference relative to ET only group) were: decreased leukocytes (+23.3%), decreased hemoglobin (+21.3%), decreased platelets (+15.1%), and decreased neutrophils (+15.0%). Grade 3 hematological abnormalities in the ribociclib + ET group (≥ 10.0% difference relative to ET only group) were: decreased neutrophils (+41.5%), decreased leukocytes (+26.8%), and decreased lymphocytes (+12.4%). The highest number of patients (in both treatment groups) with grade-4 hematological abnormalities were decreased lymphocytes (2.7% of ribociclib + ET patients and 2.3% of ET only patients) [Study O12301C EA&SU-Section 4.4.1].

Most clinical chemistry abnormalities were of low-grade. Grade 1 / 2 increased creatinine (+20.9%) were the only clinical chemistry parameter reported in a higher proportion of patients (difference ≥ 10%) who received ribociclib + ET, compared with patients who received ET only. The frequency of remaining post-baseline biochemical abnormalities was similar by group.

There were no grade 3 clinical chemistry abnormalities in ribociclib + ET group with a ≥ 10% difference relative to ET only group.

The most common grade 4 clinical chemistry abnormalities (with incidences ≥ 1.0%) reported in ribociclib + ET group were increased ALT (1.5% vs. < 0.1%) and increased urate (1.5% vs. 1.8%) [Study O12301C EA&SU-Section 3.1 and 3.2].

The FDA's Assessment:

FDA has analyzed laboratory abnormalities and generally concurs with the Applicant's analysis and assessment of clinical chemistry and hematology abnormalities. The most common laboratory abnormalities were related to myelosuppression and abnormal liver function tests.

The incidence and severity of neutropenia was markedly increased in patients who received ribociclib. While grade 1-2 neutropenia was reported in half of patients receiving ribociclib + ET compared to a third of patients receiving ET only, the most striking difference was in the incidence of higher grades of neutropenia. In the ribociclib + ET arm, 45% of patients had grade ≥3 neutropenia compared to 2% of those in the ET arm. Neutropenia as an AESI is discussed in further detail in Section 8.2.5.1.

Grade 1-2 anemia (47% vs 25%) and thrombocytopenia (28% vs 13%) were approximately twice as common in patients who received ribociclib + ET compared to those who received ET only. Grade ≥ 3 anemia and thrombocytopenia were more common with addition of ribociclib but occurred at <1% incidence in both treatment groups.

Transaminases were elevated more often in patients on ribociclib + ET. All-grade increases in ALT (ribociclib + ET 44.8% vs ET only 35.3%) and AST (44% vs 33%), as well as grade ≥3 increases in ALT (8.1% vs 1%) and AST (5.3% vs 1.1%) were more common in patients receiving ribociclib. Liver function abnormalities and hepatotoxicity are discussed in further detail as an AESI in Section 8.2.5.3.

Patients who received ribociclib in addition to ET were more likely to have all-grade increased creatinine (32.5% vs 11.4%). While almost all of these were low-grade, grade 3 increased creatinine was also more common with ribociclib (0.3% vs 0%). FDA therefore analyzed acute kidney injury (AKI) as a grouped term (consisting of PT terms: acute kidney injury, GFR decreased, renal failure, renal disorder, renal impairment, oliguria, creatinine renal clearance decreased, and azotemia). While uncommon overall, this analysis found that AKI occurred more often in patients who received ribociclib + ET (2.5% vs 0.9%). As with laboratory abnormalities, most of these AKI group term AEs were grade 1/2. Grade ≥3 AKI AEs occurred in 4 patients (0.2%) of those on ribociclib compared with none of those on ET alone. This will continue to be monitored in the postmarket setting and the USPI Warnings & Precautions updated as appropriate if more severe renal dysfunction becomes apparent with wider use.

Electrolyte abnormalities (magnesium, potassium, and calcium, both increased and decreased) were more common in patients who received ribociclib, but most were grade 1/2. Grade 3/4 electrolyte abnormalities occurred in <1% of patients. To further understand this issue, FDA performed an analysis using grouped terms to assess multiple gastrointestinal (GI) AEs. This found an increased risk of all-grade stomatitis (8% vs

1.3%), nausea (23% vs 8%), vomiting (8% vs 4%), and diarrhea (15% vs 6%). It is likely that most of the observed electrolyte abnormalities are related to poor oral intake and GI losses, though it is possible that the increased incidence of renal dysfunction may also be playing a role. Given the potential for electrolyte abnormalities, whether due to GI toxicity or renal dysfunction, to increase the risk of QT prolongation, which is a known AESI for ribociclib, chemistries should be monitored regularly per the USPI and electrolytes corrected as needed.

Vital Signs

The Applicant's Position:

No meaningful differences between the treatments groups were observed for vital signs, i.e. systolic or diastolic BP, heart rate, and body temperature. In general, median change from baseline to the lowest postbaseline median value or the highest postbaseline median value was not appreciably different by group for any vital sign [SCS Study O12301-Section 4.1].

The FDA's Assessment:

FDA agrees with the Applicant's assessment of vital signs.

Electrocardiograms (ECGs)

The Applicant's Position:

Notable ECG values are discussed in detail in Section 8.2.5.2.

Based on ECG, change in heart rate by treatment group was similar by group. Heart rate data were not analyzed from local ECGs. Overall clinical interpretation of centrally assessed ECG results at baseline compared with worse on-treatment did not identify a pattern.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. See detailed discussion of QTcF findings in the following section and as an AESI in Section 8.2.5.2.

Data:

Table 31: Clinically notable ECG values by treatment group in Study O12301C (Safety set)

QT parameter	Final iDFS analysis: 21-Jul-2023 data cut-off Ribociclib + ET N=2525 n/m (%)	ET only N=2442 n/m (%)	Overall N=4967 n/m (%)
QTcF			
New value > 450 and ≤ 480 ms	240/2477 (9.7)	66/2365 (2.8)	306/4842 (6.3)
New value > 480 and ≤ 500 ms	7/2493 (0.3)	4/2378 (0.2)	11/4871 (0.2)
New value > 480 ms	10/2493 (0.4)	4/2378 (0.2)	14/4871 (0.3)
New value > 500 ms	3/2493 (0.1)	1/2378 (< 0.1)	4/4871 (0.1)
Increase from baseline > 30 and ≤ 60 ms	462/2493 (18.5)	167/2378 (7.0)	629/4871 (12.9)
Increase from baseline > 60 ms	19/2493 (0.8)	2/2378 (0.1)	21/4871 (0.4)

Central assessments only.
Patients are counted based on any notable ECG postbaseline value.
Baseline is defined as the last assessment on or before start of study treatment. For any replicate/triplicate ECGs per timepoint, the average of these measurements would be calculated for baseline.
n=Number of patients who meet the designated criterion.
m=Number of patients at risk for a specific category. For new abnormality postbaseline, this is the number of patients with both baseline and postbaseline evaluations, and baseline not meeting the criteria. For abnormal change from baseline, it is the number of patients with both baseline and postbaseline evaluations.
N=Total number of patients in the treatment group in this analysis set.

Source: [SCS Add. Study O12301C-Table 2-24]

The Applicant's Position:

Based on central ECG assessment, clinically notable QTcF value of > 480 ms was infrequent in both groups: in the ribociclib + ET group (10 patients, 0.4%) vs. the ET only group (4 patients, 0.2%), which included 3 patients (0.1%) with a QTcF > 500 ms in the ribociclib + ET group vs. one patient (<0.1%) in the ET only group. An increase of QTcF > 60 ms from baseline was observed in 19 patients (0.8%) in the ribociclib + ET group, and in 2 patients (0.1%) in the ET only group. Of note, overall, increase in QTcF > 60 ms from baseline or QTcF >480 ms did not result in clinically relevant abnormalities and were not associated with cardiac signs or symptoms.

These ECG changes were reversible with dose interruption, and the majority occurred within the first 4 weeks of treatment. There were no reported cases of sudden death or Torsades de Pointes [CO Study O12301-Section 5.3.2].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of QT interval prolongation except as noted in the discussion below. FDA's QT-IRT committee independently confirmed the QT results based upon central assessment provided by the Applicant in Table 31.

Adding ribociclib to ET clearly increases QT interval compared to ET only. In total, based upon centrally-assessed ECGs, 481 (19%) of patients in the ribociclib + ET group had an increase in QT interval >30 ms compared with 169 (7%) of patients in the ET only group. Increases in QT interval >60 ms, while increased with the addition of ribociclib, remained uncommon overall, however, reported in 19 (0.8%) of patients on ribociclib + ET

compared with only 2 (0.1%) patients on the ET only arm based upon centrally-assessed ECGs.

Increases in QT interval to a new value >450 ms based upon centrally-assessed ECGs were also more common for patients who received ribociclib + ET compared to those randomized to ET only: 260 patients (10%) versus 75 patients (3%). Ten of these patients (0.4%) on the ribociclib + ET arm had a new value >480 ms, of whom 3 (0.1%) had a new value >500 ms; by comparison, 0.2% of patients receiving ET only had a new value >480 ms, of whom only 1 (0.1%) had a new value >500 ms.

Per FDA's QT-IRT team, when both centrally-assessed and locally-read (unscheduled) ECGs were analyzed, 8 patients (0.3%) had a >500 ms post-baseline QTcF interval value, and 50 patients (2%) had a >60 ms QTcF interval increase from baseline. (b) (4)

the review team recommends considering a consistent approach to reporting of these QTcF outliers across both indications in the USPI and has sent a comment to the Applicant to harmonize these sections in both the ribociclib USPI and the ribociclib + letrozole USPI.

Despite these clear increases in QT interval, there were not cardiac signs or symptoms reported in association with QT prolongation. AESIs potentially related to undetected QT prolongation were rare, suggesting that the lower dose of ribociclib used in the NATALEE trial, as well as the protocol-specified ECG monitoring and dose modification guidelines, were effective in mitigating the clinical risk associated with QT prolongation.

(b) (4) **the incidence of QTcF prolongation >60 ms from baseline** (b) (4)

with use of ribociclib was much lower in the NATALEE trial than in ribociclib trials in the metastatic setting, where 6% of patients using local + central results had a >60 ms increase from baseline and 1.4% had a new value >500 ms. Given that QT prolongation with ribociclib is known to be concentration-dependent, this is likely due to the lower dose of 400 mg/day used in NATALEE compared to the usual dose of 600 mg/day in the metastatic setting. Early breast cancer populations are often in better overall health than patients with metastatic breast cancer, which may also have contributed to the lower risk.

As clinically significant QT prolongation after the first 4 weeks of treatment was rare in those receiving ribociclib + ET compared to those receiving ET alone, and was not observed on any routine Cycle 2 Day 1 ECG for any patient with a normal QTcF in cycle 1, FDA agreed with the Applicant's request to remove the recommendation for routine ECG in Cycle 2 from the USPI, with additional ECGs to be performed only for patients with QT prolongation observed in Cycle 1 or as clinically indicated.

Importantly, patients with significant cardiac history were excluded from the NATALEE trial, but may end up receiving ribociclib in the postmarket setting. Clinicians should

therefore assess a patient's individual risk, based upon baseline QT interval, comorbidities, concomitant medications, and other risk factors for QT prolongation, and discuss the limitations of available data to inform shared decision-making on further ECG monitoring in patients at higher risk of developing QT prolongation.

QT prolongation as an AESI is discussed is further detail in Section 8.2.5.2.

Immunogenicity

The Applicant's Position:

Not applicable as this was not assessed nor expected.

The FDA's Assessment:

Not applicable.

8.2.5 Analysis of Submission-Specific Safety Issues

Study O12301C was properly designed to actively monitor, capture, and adequately characterize the current safety topics of interest with ribociclib in this target population in the adjuvant eBC setting.

Analyses of the Safety set from Study O12301C did not reveal any new safety signal. The current safety topics of interest with ribociclib in adults with HR-positive, HER2-negative eBC reveal a predictable and manageable safety profile with a 400 mg starting dose of ribociclib in combination with ET.

Three categories of events are discussed here (neutropenia, QT interval prolongation, and hepatobiliary toxicity); these are well characterized clinical issues associated with the use of ribociclib which, in general, can be effectively managed in the clinical setting (with dose interruption and/or dose modification).

Analysis results for the remaining AESIs are provided in [SCS Study O12301C-Section 2.6].

8.2.5.1 Neutropenia

The Applicant's Position:

Neutropenia is an important identified risk for ribociclib. This common adverse effect associated with CDK4/6 inhibition is concentration dependent, transient, and reversible. Neutropenia associated with ribociclib therapy can be clinically managed through dose modification and interruption.

Neutropenia AESI were among the most common toxicities reported (overall: 62.5% vs. 4.6%). Events were limited to (in decreasing frequency for ribociclib + ET) neutropenia (41.5%), decreased neutrophil count (24.1%), febrile neutropenia (0.3%), and granulocytopenia (0.2%).

Events of Neutropenia AESI represented the vast majority of grade ≥ 3 AEs in Study O12301C. These events had limited clinical impact, as the majority of events were asymptomatic laboratory abnormalities and completely resolved with appropriate management as per protocol.

In the ribociclib + ET group, Neutropenia AESIs were often severe (grade ≥3: 44.3%) and resulted in dose interruption (43.3%). However, AEs leading to dose adjustment (14.2% vs. 0)

and specifically AEs leading to discontinuation (1.1% vs. 0) due to neutropenia events were infrequent (ribociclib + ET vs. ET only).

Although there was a high incidence of grade ≥ 3 neutropenia AESIs, this did not translate into a clinically significant increase in risk of severe infections in patients treated with ribociclib; grade ≥ 3 infections occurred in 5.5% and 3.2% in the ribociclib + ET and the ET only treatment arms respectively. Febrile neutropenia was limited to 7 patients (0.3%) in the ribociclib + ET group: 4 patients (0.2%) required dose interruption; 2 patients (0.1%) required dose reduction and/or discontinuation of study treatment, and 1 patient (< 0.1%) had an SAE. There were no cases of febrile neutropenia in the ET only group, and there were no fatalities related to neutropenia. Based on neutrophil counts, neutropenia events were generally observed early over the course of treatment with ribociclib and their incidences did not increase over time. Management guidelines for neutropenia remain the same as in the approved label for patients with aBC [CO Study O12301-Section 5.3.1]

The FDA's Assessment:

FDA has analyzed neutropenia as an abnormal laboratory value and a grouped term AE (including PT terms neutrophil count decreased and neutropenia) and generally agrees with the Applicant's assessment.

As discussed earlier, taking into consideration both decreased neutrophils on laboratory values as well as reported adverse events of neutropenia of any grade, the majority of patients receiving ribociclib on NATALEE experienced a low neutrophil count. Neutropenia with ribociclib is concentration-dependent, and the incidence of grade ≥3 neutropenia in early breast cancer is significantly lower than that observed in the trials in metastatic breast cancer, presumably due to the lower dose of ribociclib used in the NATALEE trial.

Even with the dose of ribociclib used in the NATALEE trial, which is 200 mg lower than that used in the metastatic setting, nearly half of the patients on the ribociclib + ET arm had at least one episode of grade ≥3 neutropenia. However, despite the high incidence of neutropenia, including grade ≥3 neutropenia, it was able to be managed on study for most patients with temporary interruption of the CDK inhibitor. About 1 in seven patients required a dose reduction for neutropenia, but permanent discontinuation due to neutropenia was required in only 1% of patients. Clinically meaningful complications of neutropenia occurred more often in those receiving ribociclib but were infrequent overall; grade ≥3 infections were 2.3% more common and febrile neutropenia was 0.3% more common in patients on ribociclib + ET compared to those on ET alone. There were no deaths reported to have been associated with neutropenia on ribociclib.

The incidence and severity of neutropenia generally did not increase with time for patients over the course of the 36-month treatment, suggesting that neutropenia management guidelines used in the NATALEE trial and reflected in the USPI are appropriate to mitigate the risk. The Applicant's proposed labeling has been modified to reflect both the laboratory abnormalities and adverse events of neutropenia as this better characterizes the overall incidence and ensures that clinicians monitor absolute neutrophil count (ANC) closely and modify treatment as necessary.

While neutropenia with adjuvant ribociclib is very common and often high-grade, with the recommended monitoring and treatment interruption, dose reduction, or discontinuation as described in the USPI, the risk of serious infections attributable to neutropenia in this curative intent population who will be receiving 3 years of treatment appears to be low.

There was an increased risk of SARS-CoV-2 infection and COVID-19/COVID-19 pneumonia, including fatal cases that occurred during the on-treatment period, in patients receiving ribociclib + ET. This AE did not appear to be related to treatment-emergent neutropenia and is discussed in further detail in Section 8.2.4.

8.2.5.2 QT interval prolongation

QT prolongation is an important identified risk for ribociclib. As previously known, ribociclib prolongs the QT interval in a concentration-dependent manner. This risk is minimized by the specific dose modification guidance and ECG and serum electrolyte monitoring plan in the current label, which is considered adequate.

A comprehensive clinical safety assessment of QT prolongation is included within this dossier in a specialty safety report [QT/QTc Safety Analysis Report Study O12301C]. Per the study inclusion criteria, patients were required to have baseline QTcF < 450 ms with no significant uncontrolled cardiac disorder.

Frequency of events in the QT interval prolongation AESI were as follows in the ribociclib + ET group compared with the ET only group: all grades: 5.3% vs. 1.4%; grade ≥3: 1.0% vs 0.6%. Among the AESI grouping term, the most frequent AE by PT term was ECG QT prolonged (all grades: 4.3%, ribociclib + ET; 0.7%, ET only). Following in frequency, syncope presented infrequently and similarly by group (0.7% vs. 0.6%). There was one AE (cardiac arrest) leading to death in the ribociclib + ET group. This event occurred >30 days off ribociclib and was considered not related by the Investigator. The patient had no reported ECG/QT/QTcF abnormalities.

Overall, events within the QT prolongation AESI were uncommon and with limited clinical impact rarely requiring dose adjustment, interruption, or discontinuation (0.1%; 1.1%; 0.4% respectively) in the ribociclib + ET group.

Notable ECG values

Based on central ECG assessment, clinically notable QTcF value of > 480 ms was infrequent in both groups: in the ribociclib + ET group (10 patients, 0.4%) vs. the ET only group (4 patients, 0.2%), which included 3 patients (0.1%) with a QTcF > 500 ms in the ribociclib + ET group vs. one patient (<0.1%) in the ET only group. An increase of QTcF > 60 ms from baseline was observed in 19 patients (0.8%) in the ribociclib + ET group, and in 2 patients (0.1%) in the ET only group. Of note, overall, increase in QTcF > 60 ms from baseline or QTcF >480 ms did not result in clinically relevant abnormalities and were not associated with cardiac signs or symptoms.

These ECG changes were reversible with dose interruption, and the majority occurred within the first 4 weeks of treatment. There were no reported cases of sudden death or Torsades de Pointes.

Time to event analyses: Median time-to-onset of ECG QT prolongation grade ≥2 events was 0.5 months (range: 0.5 to 1.5), which correlates to approximately Cycle 1 Day 15 per protocol-

scheduled monitoring in the ribociclib + ET group, compared with 1.4 months (range: 0.9 to 2.8), or approximately Cycle 2 Day 15 per protocol-scheduled monitoring in the ET only group. Of note, the majority of notable QTcF values were observed on Cycle 1 Day 15.

Median time-to-onset of ECG QT prolongation grade ≥3 events was 1.4 months (range: 0.5 to 1.5) in the ribociclib + ET group, compared with 1.9 months (range: 1.9 to 1.9) in the ET only group.

Of note, there was minimal change in notable QTcF values at Cycle 2 Day 1 compared to baseline (mean change from baseline at Cycle 2 Day 1 was 0.5 ms) in the ribociclib + ET group. This minimal QTcF prolongation is expected due to the 7 days off of dose, where the concentration of ribociclib is expected to be low, based on the 3-weeks on/1-week off ribociclib dosing schedule. This is further supported by the fact that no first occurrences of notable ECG values have been observed at this timepoint in ribociclib + ET group.

Management recommendations: As described above, ECG prolongation events were of low incidence (1.0% grade ≥ 3 QT ECG prolonged AESI; 0.4% QT interval > 480 ms) without associated cardiac signs or symptoms in ribociclib + ET group. The mean QTcF change (ΔQTcF) from baseline was 9.5 ms at Cycle 1 Day 15 2 hours postdose, which corresponds to steady state ribociclib concentration. The mean change from baseline was 0.5 ms at Cycle 2 Day 1 predose ECG, which corresponds to the lowest ribociclib concentration, as expected, following the 7 days off dose based on the 3-weeks on/1-week off dosing schedule. In view of these data from Study O12301C, Novartis proposes ECG monitoring for patients with eBC at baseline before initiating treatment, and approximately Cycle 1 Day 14 (steady-state ribociclib concentration), with additional ECGs as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

Consistent with the proposal for patients with eBC, Novartis also proposes to revise the existing risk minimization measures for management of risk of QT interval prolongation in patients with aBC (ie, to remove the requirement for ECG monitoring at the beginning of the second cycle/Cycle 2 Day 1), based on the low incidence of QT prolongation events at Cycle 2 Day 1, which corresponds to the low concentration of ribociclib and minimal change in QTc interval from baseline (ΔQTcF), median time to first occurrence of Grade 2/3/4 QT prolongation of 2.1 weeks which approximates Cycle 1 Day 15, and no clinical evidence among patients with notable ECG at Cycle 1 Day 15 and Cycle 2 Day 1 that mandating Cycle 2 Day 1 QTcF monitoring for all patients would have provided additional benefit to support managing the risk of QT prolongation in patients with aBC [SCS Add. Study O12301C-Appendix 4].

Other risk mitigation measures for QT prolongation including dose modification guidance, baseline threshold of QTcF <450 ms, monitoring of electrolytes, and assessment of relevant medical history and concomitant medications are included in the proposed label. More details are provided in [QT/QTc Safety Analysis Report Study O12301C] included in this submission.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment except as noted below.

The median time to grade ≥2 QT prolongation, a QTc of 481-500 ms, was 0.5 months (range: 0.5 to 1.5), which corresponds with the cycle 1 day 15 ECG. Although there were cases of QT prolongation beyond Cycle 1, there were no patients with a first occurrence of

QTc >480 ms at the Cycle 2 Day 1 ECG, which follows a week off of ribociclib in the 3 weeks on, 1 week off dosing regimen and therefore corresponds to lower ribociclib exposure.

No patients with documented QT prolongation were symptomatic, and treatment interruption (0.8%), dose reduction (0.1%), and discontinuation (0.1%) due to QT prolongation were rare in patients treated with ribociclib + ET. There were no reported cases of Torsades de pointes (TdP).

Although more subjects experienced SAEs that could potentially be related to QT prolongation (though QT prolongation was not documented in these cases) in the ribociclib + ET group than the ET only group, based upon FDA's review of CRFs and patient narratives, most were considered unlikely to be related to ribociclib, either due to the time elapsed since last exposure to ribociclib and/or alternative explanations. One patient in the ribociclib + ET group had treatment discontinuation due to grade 2 ventricular tachycardia that the Investigator and FDA suspected was related to ribociclib, although concomitant medications may have contributed to the risk.

FDA reviewed CRFs and detailed narratives provided by the Applicant and provides brief summaries below for the following patients with SAEs that may occur with QT prolongation, even though no QT prolongation was documented:

Participant ID# (b) (6) is a 43-year-old female with a past medical history of grade 3 obesity who was randomized to the ribociclib + ET arm. At screening, her vital signs and ECG were normal. Electrolytes and ECGs were within normal range throughout the study. Ribociclib was permanently discontinued on Study Day 314 due to the physician's decision, resulting from concern over incorrect use of study medication as her diaries and pill counts were not consistent with one another on two occasions. Anastrozole was discontinued the following month with no explanation available. On Study Day 365, 51 days after the last dose of ribociclib, she had grade 5 cardiac arrest. Concomitant adverse events at the time were arthralgia (grade 1), asthenia (grade 1), memory impairment (grade 1), and depression (grade 1). No other information was available on the primary and secondary cause of death as well as other comorbidities at the time of death. The Investigator did not suspect a relationship between cardiac arrest and the study medications. FDA considers the cardiac arrest unrelated to study drug as cardiac arrest occurred more than 7 weeks after the last dose of ribociclib.

Participant ID# (b) (6) is a 61-year-old female randomized to ribociclib + ET. She had completed 36 months of treatment with ribociclib on Study Day 1085 and was receiving letrozole monotherapy per standard of care. On Study Day 1239, she presented to the emergency department with grade 3 dyspnea and grade 3 hypotension. An ECG showed grade 3 atrial flutter and tachycardia with a heart rate of 160, and she was admitted to the ICU. On Study Day 1240, she experienced grade 2 nausea and grade 3 hypoglycemia. Labs at that time revealed grade 3 creatinine of 3.4 mg/dL, and she was diagnosed with grade 3 acute kidney injury. She also had grade 4 increase in ALT and AST as well as grade 3 increase in total bilirubin. An echocardiogram revealed acute heart failure with left ventricular ejection fraction (LVEF) of 15% with severe global hypokinesis. Her AST and ALT continued to be elevated (grade 4), as did her creatinine and total bilirubin (both grade 3) over the next 48 hours. On Study Day 1243, she experienced grade 5 cardiac arrest

and died of cardiogenic shock. FDA considers the cardiac arrest unrelated to study drug as it occurred more than 5 months after the last dose of ribociclib.

Participant ID # (b) (6) is a 40-year-old premenopausal female who was randomized to ribociclib + ET. On day 343 of the study, she collapsed at home and was diagnosed with grade 3 syncope. A head CT showed new brain metastases. Concomitant AEs at that time were grade 1 leukopenia and grade 2 lymphopenia. Study treatment was permanently discontinued, and she died due to disease progression 250 days after the last dose of study drug. While a contribution of ribociclib to syncope cannot be excluded based on the available information, FDA considers the SAE of syncope most likely to have been caused by new brain metastases.

Participant ID (b) (6) is a 39-year-old female randomized to ribociclib + ET. On Study Day 504, she developed weakness and dyspnea. On Study Day 505, she developed grade 3 abdominal pain, grade 2 pyrexia, grade 3 syncope, and grade 3 circulatory collapse. She tested positive for SARS-CoV-2 and was hospitalized with grade 3 COVID-19. Her electrolytes, ANC, and WBC were normal, and CRP was elevated at 26.3. Head CT, thoracic CT, and ECG were normal. Abdominal CT showed grade 1 increase in adipose tissue density. She was treated with electrolytes and low molecular weight heparin for the syncope and circulatory collapse, levofloxacin and erdosteine for COVID-19, and metamizole for fever. While a contribution of ribociclib cannot be excluded based on the available information, FDA judges the SAE of syncope more likely to have been caused by COVID-19.

Participant ID# (b) (6) is a 49-year-old female with no PMH. She was diagnosed with Stage IIIA right breast cancer on (b) (6) and treated with neoadjuvant chemo with AC-T, mastectomy, ALND, radiotherapy to the chest wall and regional nodes. Her ECG and QT interval were normal at baseline and throughout the study. She was randomized to ribociclib + letrozole and on Study Day 18, developed grade 2 vomiting and diarrhea and grade 3 syncope, which resolved the same day. Concurrent AEs were grade 1 neutropenia. Ribociclib was interrupted from Study Day 19 and restarted at reduced dose from Study Day 29 to 49 and then subsequently re-increased to Study Day 57. There were no further syncopal episodes reported for her. The patient subsequently experienced distant recurrence with liver metastases on Study Day 11 and discontinued treatment. The Investigator suspected a relationship between the AESI of syncope and ribociclib. FDA concurs that syncope was most likely related to the vomiting and diarrhea caused by ribociclib, though did not appear to be associated with QT prolongation.

Participant ID # (b) (6) is a 69-year-old postmenopausal female randomized to ribociclib + ET who had grade 2 hypokalemia at screening. On Study Day 29, she had grade 1 dry eye, grade 3 neutrophil count decreased, grade 2 platelet count decreased, and grade 3 white blood cell count decreased (grade 3), and ribociclib was held. On Study Day 32, she experienced grade 3 syncope and was hospitalized. Vital signs were notable for BP of 92/57 mm Hg. Electrolytes were normal other than grade 1 hyponatremia. Chest x-ray, head CT, and ECG were all normal. She was treated with normal saline, and no further syncopal episodes occurred. While a contribution of ribociclib to syncope cannot be excluded based on the available information, FDA judges the SAE of syncope more likely to have been

caused by hypovolemia given the low blood pressure at presentation, improvement with rehydration, and the absence of any QT prolongation or arrhythmia.

Participant ID# (b) (6) is a 60-year-old postmenopausal female randomized to ribociclib + ET. Of note, she received study-prohibited medications of azithromycin on Study Day 100 and levofloxacin from Study Day 107 to Day 114. On Study Day 100, she experienced grade 3 non-cardiac chest pain and syncope and was hospitalized. It was reported that the same day, she felt unwell with cough productive of green sputum, night sweats, lightheadedness, and pain in the left arm, and she collapsed with syncope with walking. She regained consciousness immediately and reported chest discomfort. Her blood pressure was 153/78, and the ECG was normal. An echo showed 60-65% with grade 1 left ventricular diastolic dysfunction, moderate aortic valve regurgitation, mildly calcified aortic valve leaflets, a mildly dilated right ventricle, trace tricuspid valve regurgitation, and a trivial pericardial effusion. Ribociclib was temporarily interrupted from Study Days 100 to 103. The AEs resolved on the same day, and she was discharged on Study Day 104. FDA considers it possible that ribociclib caused or contributed to the SAE of syncope, however she also had received two prohibited concomitant medications in the three days leading up to, and on the day of, the syncope SAE. The timing of azithromycin relative to syncope is not clear (both were on Study Day 100, and azithromycin was listed as having been given for "prophylaxis"), but FDA notes that azithromycin also has a W&P for QTc prolongation.

Participant ID # (b) (6) is a 40-year-old postmenopausal female randomized to ribociclib + ET. On Study Day 935, she had grade 2 hypertension. Ribociclib was temporarily interrupted, and no treatment was reported. On Study Day 950, she had grade 1 palpitations. No action was taken with ribociclib and anastrozole due to this event. On Study Day 998, she had grade 2 ventricular tachycardia (no other ECG details including QT interval available), and ribociclib was permanently discontinued. No action was taken with anastrozole. Palpitations resolved on Study Day 1005. Anastrozole was permanently discontinued on Study Day 1008 per physician's decision. Concomitant AEs at the time of the AE were grade 1 nausea, constipation, arthralgia, and insomnia. Concomitant medications at time of AE onset included valacyclovir for herpes simplex, loratadine for allergic rhinitis, duloxetine hydrochloride, bupropion for affective disorder, and lorazepam and melatonin for insomnia. Both ventricular tachycardia and hypertension were listed as ongoing at the time of the report. The Investigator suspected a relationship between grade 2 ventricular tachycardia and the study medication ribociclib. FDA also considers the relationship to ribociclib probable but notes the timing of the first report of palpitations and subsequently arrhythmia at 31-33 months into study treatment is unexpected as most QT prolongation occurs early in treatment. In addition, bupropion is associated with increased risk of QT prolongation and ventricular arrhythmias, and ventricular arrhythmias have also been reported with duloxetine, mostly in patients with other risk factors. It is possible that the combination of these medications contributed to the AE.

With appropriate patient selection, including baseline QTcF <450 ms and assessment of risk based upon personal/family history, as well as risk mitigation, including avoidance of other QT prolonging medications, monitoring/correction of electrolyte abnormalities, and dose modification as needed, FDA concurs that routine ECG monitoring for all patients on Cycle 2 Day 1 is not required. The Cycle 1 Day 15 ECG, which occurs at steady state concentration, may be used by clinicians in combination with the above elements of the history and laboratories to identify the subset of patients on ribociclib for whom additional ECG monitoring beyond Cycle 1 is necessary. Patients with QT prolongation observed on the Cycle 1 Day 15 ECG, as well as patients at increased risk of QT prolongation or arrhythmia based upon medical history or concomitant medications, should have continued ECG monitoring beyond Cycle 1. The USPI will be updated to reflect this modified recommendation.

While there was no difference in the incidence or severity of tachycardia between the two groups, FDA noted that palpitations were reported more commonly in patients on the ribociclib + ET arm (3.4%) compared to those on the ET only arm (1.1%). To evaluate for arrhythmias that may have occurred without QT prolongation or with QT prolongation that was not captured on ECG, FDA also analyzed arrhythmia as a grouped term (consisting of atrial fibrillation, electrocardiogram QT prolonged, Wolff-Parkinson-White syndrome, supraventricular tachycardia, sinus bradycardia, sinus arrhythmia, electrocardiogram repolarization abnormality, extrasystoles, arrhythmia, supraventricular extrasystoles, atrioventricular block first degree, ventricular extrasystoles, arrhythmia supraventricular, sinus tachycardia, atrial flutter, atrial tachycardia, electrocardiogram P wave abnormal, bundle branch block right, atrioventricular block, tachyarrhythmia, electrocardiogram PR prolongation, ventricular tachycardia, long QT syndrome, TdP, and bundle branch block left) and found an increased incidence of all-grade AEs in the ribociclib + ET group (6% vs 3.3%). While the majority of these were grade 1/2, the incidence of grade ≥ 3 AEs in this grouped term was also doubled with ribociclib use (0.6% vs 0.3%). As discussed earlier in Section 8.2.4, electrolyte abnormalities were more common in patients on ribociclib + ET, and while most were grade 1/2, it is possible that this contributed.

It is important to note that patients with significant cardiac history were excluded from NATALEE (as well as trials in the metastatic setting) but may be exposed to ribociclib in the postmarket setting. In addition, nearly one in five patients on the NATALEE trial received at least one dose of a prohibited concomitant medication, including many medications prohibited due to increased risk of QT prolongation. As discussed above in the narratives in this section, although adverse cardiac events potentially related to concomitant medication use occurred on the NATALEE trial, they appear to have been rare.

Attention to reports of arrythmia AEs, especially TdP, ventricular arrhythmias, or sudden cardiac death, will be especially important for postmarketing pharmacovigilance given the broader introduction of ribociclib in a curative intent setting. No cases of TdP have been

reported to date. If clinically significant QT prolongation is identified in patients with early breast cancer in the postmarket setting, consideration of a labeling change to add back routine ECG monitoring in Cycle 2, but at Day 15 rather than Day 1, given the 3 week on, 1 week off dosing regimen, is recommended.

8.2.5.3 Hepatobiliary toxicity

Hepatobiliary toxicity is an important identified risk for ribociclib. The majority of hepatobiliary AESIs were laboratory findings of elevated ALT/AST concentrations, which tended to occur early during treatment and were manageable with protocol dose management guidance specific for hepatotoxicity. Hepatobiliary AESIs were one of the most common grade ≥ 3 AEs in Study O12301C, and the most common reason for treatment discontinuation but were effectively manageable with dose adjustments, and were reversible.

In Study O12301C, the proportion of patients with hepatobiliary toxicity grouped AEs was greater in the ribociclib + ET group vs. the ET only group (26.4% vs. 11.2%); likewise the proportions of patients with grade ≥3 events were 8.6% and 1.7%, respectively. The most frequently reported events in this AESI category included: ALT increased (19.5% vs. 5.6%) and AST increased (16.9% vs. 5.7%) [SCS Add. Study O12301C-Table 2-19]. Importantly, these 2 PTs were amongst the most common [SCS Add. Study O12301C-Table 2-3] and more severe events [SCS Add. Study O12301C-Table 2-4] that were assessed with causal relationship to study treatment by the Investigator [SCS Add. Study O12301C-Table 2-5] in the ribociclib + ET group. All remaining PTs in the hepatobiliary toxicity grouped AEs were reported at < 5.0% in either group.

No noteworthy differences were observed since IA3. No additional patients with DILI or confirmed Hy's Law were identified since the primary analysis/IA3 [SCS Add. Study O12301C-Section 2.6.7].

- Within the Hepatobiliary toxicity AESI, DILI was reported for 9 patients (0.4%) and of these, 5 were grade ≥ 3. Of these 9, 8 patients' events resolved as of DCO [Study O12301C Primary Analysis CSR-Listing 16.2.7-1.1]. All 9 patients with DILI are discussed in [Study O12301C Primary Analysis CSR-Section 14.3.3], and were in the ribociclib + ET group.
- There were 8 clinically confirmed Hy's Law cases, including 4 of the 9 patients with DILI. All 8 patients were in the ribociclib + ET treatment group (n=2524). Importantly, most (6 out of 8 patients) completely recovered after discontinuation of ribociclib; 2 patients had improvement in lab values after ribociclib discontinuation, albeit mild lab abnormalities were still as of DCO (1 patient, grade 2 elevated TBL; 1 patient, grade-1 elevated AST/ALT and grade-2 elevated TBL) [Study O12301C SCS-Section 2.6.6].

When assessing Hepatobiliary toxicity AESI as grade ≥ 3 AEs, SAEs, AEs leading to discontinuation, dose adjustment, and/or dose interruption, increased ALT (7.6%, 0.4%, 7.1%, 1.9%, and 10.1%, respectively) and increased AST (4.7%, 0.2%, 2.8%, 0.6%, and 6.8%,

respectively) were often the most frequent events in the ribociclib + ET group [SCS Add. Study O12301C-Appendix 1-Table 14.3.1-6.2].

There were no on-treatment deaths in the Hepatobiliary toxicity AESI [SCS Add. Study O12301C-Table 2-19].

Time-to-event analyses: Median time-to-first occurrence of grade ≥ 3 elevated ALT/AST was 2.8 months (range: 0.36 to 33.15) in the ribociclib + ET group, compared with 12.5 months (range: 0.46 to 33.28) in the ET only group [SCS Study O12301C-Appendix 1-Table 14.4-4.1], [SCS Study O12301C- Figure 2-6]. The estimated median duration of grade 3 or higher AST or ALT elevations (recovering to ≤ grade 2) was 0.7 months (95% CI: 0.7, 0.9) in the ribociclib + ET group and 2.2 months (95% CI: 1.2, 2.8) in the ET only group [Study O12301C Primary Analysis CSR- Table 14.3-6.2]

Management recommendations: Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. Management guidelines remain the same as in the approved label for patients with aBC.

The FDA's Assessment:

FDA has analyzed hepatobiliary AEs and laboratory abnormalities and generally agrees with the Applicant's assessment with the following additional comments.

Hepatobiliary AEs were much more common with addition of ribociclib to ET. In FDA's analysis of liver function test AEs (as a grouped term consisting of elevation in one or more of: AST, ALT, GGT, alkaline phosphatase, and blood bilirubin), 26.4% of participants on the ribociclib + ET arm had a liver function test abnormality, of which 8.6% were grade ≥3. This is a significant increase compared to the ET only arm where only 11.2% had a liver function abnormality, of which 1.7% each were grade ≥3. Most were increases in transaminases. An FDA analysis of hepatotoxicity AEs (a grouped term consisting of PT of hepatotoxicity, drug-induced liver injury (DILI), autoimmune hepatitis, and hepatic cytolysis) was also performed and similarly identified an increased incidence of all-grade (1.4% vs 0.5%) as well as grade ≥3 hepatotoxicity AEs (0.7% vs <0.1%) in the ribociclib + ET arm compared to the ET only arm.

The median time to first occurrence of grade 3/4 elevated transaminases was 2.8 months on the ribociclib + ET arm, although cases of grade 3/4 transaminase elevation occurred as early as 0.4 months and as late as 33 months into treatment.

Hepatobiliary SAEs were rare overall but clearly increased for those receiving ribociclib (1.0% vs 0.2%). Liver function test abnormalities, most commonly elevated transaminases, resulted in treatment interruption of ribociclib in 12.4% of patients, dose reduction in 2.6% patients, and permanent discontinuation in 8.9% of patients. With these treatment modifications according to the protocol, the median duration of grade 3/4 elevated transaminases in the ribociclib + ET arm was 0.7 months, and there were no on-study deaths attributed to hepatobiliary toxicity, indicating that instructions in the agreed upon USPI regarding liver function abnormalities appear adequate to monitor and mitigate this

risk for most patients. For the patients who had clear DILI and met clinical criteria for Hy's Law as discussed below, despite ribociclib discontinuation, LFT abnormalities often took months to resolve, and rare patients were left with persistent, albeit stable to improving, LFT abnormalities as discussed below.

An AE of drug-induced liver injury (DILI) was reported in 9 patients (0.4%), including five (0.2%) grade 3/4 cases, on the ribociclib + ET arm. As of the final iDFS analysis, there were 15 patients (0.6% of ribociclib +ET group vs <0.1% of ET only group) whose LFT data met *biochemical* Hy's Law criteria, defined as AST/ALT >3x upper limit of normal (ULN) + total bilirubin >2x ULN without alkaline phosphatase >2x ULN. Of these, 8 patients (0.3%) had *clinically-confirmed* Hy's Law, with no satisfactory alternative explanation for the LFT abnormalities, including 4 cases not captured in the DILI group above.

In total, 13 patients (0.5%) on the ribociclib + ET arm had DILI of all grades and/or clinically-confirmed Hy's Law. By comparison, there were no cases (0%) of DILI and/or clinically-confirmed Hy's Law reported on the ET only arm. As of the data cutoff, 8 out of 9 patients with DILI reported, and 6 out of the 8 patients with clinically-confirmed cases of Hy's Law, had recovered. The remaining patients had persistent but improved liver function abnormalities. There were no fatal cases of DILI or Hy's Law reported.

CRFs and Applicant's narratives for patients with grade ≥3 or SAEs of DILI or clinically confirmed cases of Hy's Law have been reviewed, and cases of DILI, whether or not they met clinical criteria for Hy's Law, judged by FDA to be related to ribociclib are discussed below.

Participant ID# (b) (6) is a 51-year-old white female without significant PMH except cholecystectomy who had pathological stage IIIC right breast cancer diagnosed (b) (6) . She had right mastectomy, ALND, radiotherapy to the chest wall and nodes, and adjuvant AC-T. She was randomized to letrozole + ribociclib. At baseline, her AST and ALT were grade 1, alkaline phosphatase and bilirubin were normal. On Study Day 57, she had worsening of AST and ALT to grade 2 with grade 1 alkaline phosphatase and normal bilirubin. Ribociclib was discontinued on Study Day 58, but AST and ALT worsened to grade 3 with grade 1 alkaline phosphatase with normal bilirubin. On Study Day 74, she reported grade 1 fatigue and ALT was found to have worsened to grade 4 with persistent grade 3 AST and grade 1 alkaline phosphatase. Total bilirubin was grade 1. On Study Day 75, a CT scan of the abdomen and pelvis showed no liver metastases or hepatic steatosis, and letrozole was interrupted. On Study Day 85, she had a liver biopsy that showed acute hepatitis with moderate portal and lobular inflammation consistent with DILI, and she was diagnosed with DILI. A full workup for autoimmune and infectious causes of hepatic dysfunction found only EBV IgG and CMV IgG were positive. Her LFTs began to improve on Study Day 111, and letrozole was restarted on Study Day 113. Her abnormal bilirubin was resolved on Study Day 124, elevated AST was resolved on Study Day 131, and elevated ALT was resolved on Study Day 172. The patient met clinical criteria for Hy's Law. The investigator, Applicant, and FDA all agree that DILI was due to ribociclib.

Participant ID# (b) (6) is a 64-year-old female with PMH of hepatic cysts who was diagnosed with Stage IIB breast cancer on (b) (6). She had right mastectomy and ALND, radiotherapy to the chest wall, TC chemotherapy, and was randomized to letrozole and ribociclib. At baseline, her LFTs were all normal. On Study Day 84, she had grade 1 ALT and AST. No action was taken. On Study Day 91, ALT and ALT had worsened to grade 3 and she reported grade 1 abdominal distention. Ribociclib and letrozole were permanently discontinued on Study Day 94 due to the LFT abnormalities. An abdominal US showed diffuse moderate hepatic steatosis with no focal damage. LFTs began to improve on Study Day 99, but subsequently worsened to grade 4 by Study Day 120. She was treated with steroids and underwent liver biopsy that showed abundant inflammatory, polymorphic, portal, and lobular infiltrate with mild hepatocyte necrosis, suggesting active cytolytic hepatitis. LFTs slowly improved with no other treatment. AST resolved as of Study Day 192, and ALT was resolved as of Study Day 234. Bilirubin and alkaline phosphate remained normal throughout, and therefore the case did not meet Hy's Law criteria for DILI. The investigator, Applicant, and FDA all agree that DILI was due to ribociclib.

Participant ID# (b) (6) is a 48-year-old female with no relevant PMH who was diagnosed with Stage IIA right breast cancer on (b) (6). She was treated with lumpectomy, ALD, breast radiotherapy, and adjuvant chemo with EC-T. She was randomized to goserelin and letrozole + ribociclib. At baseline, her LFTs were normal. On Study Day 54, she had grade 1 AST and ALT with normal alkaline phosphatase and bilirubin. On Study Day 83, she had grade 1 anorexia, nausea/vomiting, fatigue, hypocolia, choluria, and skin rash and was found to have grade 4 increase in AST and ALT with grade 2 total bilirubin, grade 1 alkaline phosphatase, and grade 3 GGT. Ribociclib was permanently discontinued on Study Day 84, and letrozole/goserelin was interrupted on Study Day 83. She had negative tests for viral and autoimmune causes of hepatitis, and an abdominal ultrasound showed no cholestasis. On Study Day 98, she had a liver biopsy that showed ribociclib-induced drug toxicity. She was treated with steroids, and letrozole/goserelin were restarted on Study Day 118. AST, ALT, bilirubin, and alkaline phosphatase were resolved as of Study Day 139. This case was consistent with DILI and met Hy's Law criteria. The Investigator, Applicant, and FDA all agree that DILI was due to ribociclib.

Participant ID# (b) (6) is a 56-year-old female with PMH of dyslipidemia. She was diagnosed with Stage IIIC breast cancer on (b) (6), and treated with neoadjuvant chemo with AC-T, right mastectomy, ALND, radiotherapy, and began letrozole and goserelin with ribociclib. At screening, her alkaline phosphatase was grade 1 and other LFTs were normal. She received prohibited medication simvastatin for dyslipidemia on the same day she began ribociclib and letrozole. On Study Day 112, she had grade 3 ALT, grade 2 AST, grade 1 alkaline phosphatase, and grade 3 DILI. Ribociclib was interrupted on Study Day 113 (last dose was on Study Day 105) and never restarted. On Study Day 119, AST worsened to grade 3, ALT to grade 3. Testing for Hepatitis A was inconclusive per hepatology. On Study Day 163, AST and ALT worsened to grade 4, GGT was grade 2, alkaline phosphatase was grade 1, and total bilirubin was grade 1. On Study Day 168,

endocrine therapy was interrupted. The patient received steroids for DILI. AST improved to grade 2 and ALT to grade 2 on Study Day 184. Endocrine therapy was discontinued on Study Day 209 due to DILI (last dose received on Study Day 167). The patient discontinued the study per physician's decision on Study Day 211. There was no liver biopsy or report of abdominal imaging. As of the last available labs, the patient had residual grade 1 AST and grade 2 ALT, which were consistently improving over the preceding 3 weeks of labs. The Investigator, Applicant, and FDA considered DILI probably due to ribociclib, though it is possible that letrozole also contributed. This case met clinical criteria for Hy's Law.

Participant ID# (b) (6) is a 60-year-old female with PMH of hepatitis B, hypertension, hypothyroidism, and obesity. She was diagnosed with Stage IIB breast cancer on (b) (6), and treated with neoadjuvant EC-T, left mastectomy, ALND, radiation, and began treatment with letrozole + ribociclib. At baseline, her ALT was grade 1 and other LFTs were normal. On Study Day 85, she had grade 1 LDH and grade 1 ALT with other LFTs normal. On Study Day 113, ALT was grade 2, AST was grade 1. No action was taken with her study meds. On Study Day 140, her LDH was grade 2, both AST and ALT were grade 3, GGT was grade 1, and alkaline phosphatase and total bilirubin were normal. Ribociclib was discontinued due to the LFTs on Study Day 133, and the last dose of anastrozole was Study Day 140. On Study Day 148, she developed grade 1 abdominal discomfort, with grade 3 AST, ALT, and LDH, grade 1 GGT and tested positive for Hepatitis B. An abdominal US on Study Day 149 showed changes in the liver. On Study Day 162, AST, ALT, and LDH worsened to grade 4, and total bilirubin was increased grade 2 with grade 1 alkaline phosphatase elevation. The patient was diagnosed with grade 4 DILI the same day and hospitalized on Study Day 150. She received steroids, ursodeoxycholic acid, pantoprazole, and calcium carbonate for DILI. On Study Day 158, her ALT improved to grade 3, AST improved to grade 2, and she was discharged. On Study Day 173, her LDH, ALT, and AST were grade 1, and total bilirubin was grade 2. Two months later, she developed recurrence in the skin and chest wall, followed by biopsy-confirmed distant metastatic disease in the lung/pleura. She subsequently withdrew consent from further participation in the study. Abdominal discomfort, LDH, ALT, GGT, and bilirubin increased were all considered ongoing, but labs were stable from EOT to until her withdrawal of consent approximately four months later. The Investigator, Applicant, and FDA agreed that ribociclib +/- anastrozole caused the DILI. This case met clinical criteria for Hy's Law.

Participant ID# (b) (6) is a 60-year-old female with PMH of obesity and hypertension. She was diagnosed with a right Stage IIA breast cancer on (b) (6), and treated with lumpectomy, SLNB, and breast radiotherapy. She received no chemotherapy. She was randomized to ribociclib and letrozole. At screening, her LFTs were normal. On Study Day 85, she had grade 2 ALT, grade 1 AST, and normal alkaline phosphatase, bilirubin, and GGT, as well as grade 3 neutropenia, and ribociclib was interrupted. On Study Day 94, her ALT and AST had worsened to grade 3, while other LFTs remained normal. Ribociclib was discontinued (patient's last dose was actually reportedly Study Day 77). On Study Day 108, she experienced grade 3 fatigue and abdominal pain with grade 1 chromaturia and

ALT worsened to grade 4 with grade 1 alkaline phosphatase and normal bilirubin. Tests for viral hepatitis were negative. On Study Day 120, AST worsened to grade 4, GGT was grade 3, alkaline phosphatase was grade 1, and while total bilirubin was normal, direct bilirubin was grade 2. Total bilirubin worsened to grade 2 with direct bilirubin of grade 3 on Study Day 127. An abdominal ultrasound showed no liver metastases and some thickening of the wall of the gall bladder. Hepatology diagnosed the patient with grade 3 DILI, and a liver biopsy was consistent with drug-induced hepatopathy. Treatments were somewhat unclear but included N-acetylcysteine. LFTs gradually improved to grade 2 or less by 34 days after end of treatment, and all LFTs were normal by approximately 7.5 months after end of treatment. The Investigator, Applicant, and FDA all agree that DILI was due to ribociclib. This case satisfied clinical criteria for Hy's Law.

Participant ID# (b) (6) is a 64-year-old female with PMH of hypertension who was diagnosed with Clinical Stage IIB right breast cancer on (b) (6). She was treated with neoadjuvant EC-T, mastectomy and ALND, and adjuvant therapy with tamoxifen. She was randomized to receive letrozole + ribociclib. At baseline, her LFTs were normal. On Study Day 29, she had grade 1 ALT and AST. By Study Day 43, ALT was grade 3 and AST was grade 2. Ribociclib was discontinued on Day 44. She was treated with arginine aspartate, Silybum marianum, and Essentials Max (herbal preparations). On Study Day 57, AST worsened to grade 3. On Study Day 84, ALT worsened to grade 4, AST remained grade 3, GGT was grade 3, and total bilirubin and alkaline phosphatase were grade 1. She was diagnosed with DILI. Letrozole was continued. On Study Day 86, she had viral hepatitis serologies that were negative and an abdominal MRI and CT were normal. LFTs fluctuated but by Study Day 141, ALT was grade 2, AST was grade 1, and bilirubin was normal. DILI was reported as resolved with all LFTs normal as of Study Day 337. Letrozole was given in an ongoing fashion, and ribociclib was never restarted after the last day on Study Day 43. Of note, she did have a subsequent episode of grade 1 AST and ALT, again treated with herbal preparations, which were reported as resolved as of Study Day 505. The Investigator suspected a relationship between DILI and ribociclib. The Applicant did not given that LFTs were again elevated long after treatment with ribociclib. FDA considers it probable that the events were due to ribociclib. The case did not meet Hy's Law criteria.

Participant ID# (b) (6) is a 49-year-old female with a PMH of hypertension, pancreatitis, and hepatic steatosis. She was diagnosed with Stage IIIC right breast cancer on (b) (6) and treated with mastectomy, ALND, chest wall radiotherapy, and adjuvant chemo with Abraxane/Cytoxan. At baseline, her ALT and GGT were grade 1 and the other LFTs were normal. She began goserelin, letrozole, and ribociclib. From Study Day 43 to 450, ALT fluctuated from grade 1 to grade 3 and AST from grade 1 to grade 2 with no abnormalities in total bilirubin or alkaline phosphatase. Ribociclib was interrupted from Study Day 44 to 68 and dose reduced on Study Day 29. She was treated with diammonium glycyrrhizinate, Silybum marianum, glutathione, polyene phosphatidylcholine, and glycyrrhizin injection. On Study Day 85, she had grade 2 ALT and grade 1 AST, and ribociclib was discontinued on Study Day 87. On Study Day 113, ALT was grade 1 and

AST was resolved, and on Study Day 140, ALT was resolved. The Investigator, Applicant, and FDA all agreed LFT abnormalities were due to ribociclib, though this case did not meet Hy's Law criteria.

Participant ID # (b) (6) is a 58-year-old female with PMH of hepatic cyst and hepatic steatosis. She was diagnosed with Stage IIB right breast cancer on (b) (6) and treated with neoadjuvant liposomal doxorubicin, paclitaxel, and cisplatin, mastectomy, ALND, postmastectomy radiotherapy and randomized to letrozole + ribociclib. At baseline, her LFTs were normal. On Study Day 43, she had grade 2 AST and grade 3 ALT. She was supposed to interrupt ribociclib but inadvertently continued until Study Day 49, which was her last dose of ribociclib on study. Letrozole was continued. On Study Day 66, she had grade 2 abdominal discomfort and grade 1 creatinine, grade 2 ALT, grade 3 ALT, grade 1 GGT, and normal alkaline phosphatase and total bilirubin and was admitted. An abdominal ultrasound showed hepatic steatosis and hepatic cyst. An abdominal CT showed uneven liver density and low-density shadow in the right hepatic lobe. On Study Day 71, her ALT and AST and GGT were grade 1 and alkaline phosphatase and total bilirubin were normal. On Study Day 77, ALT was grade 1, AST and GGT were grade 2, and alkaline phosphatase and total bilirubin remained normal. On Study Day 87, ALT was grade 1, AST was grade 2, total bilirubin was grade 2, GGT was grade 3, and alkaline phosphatase was normal, and she was diagnosed with DILI, grade 3. This worsened to DILI, grade 4 on Study Day 108 with grade 1 ALT, grade 1 alkaline phosphatase, grade 3 GGT, and grade 4 total bilirubin. She was re-hospitalized on Study Day 110 with concomitant cholecystitis. She received many medications including several herbal products and a few prohibited medications. An MRCP on Study Day 114 showed diffuse abnormal signal in the liver parenchyma suggestive of liver damage. No viral serologies or biopsy were reported. DILI improved to grade 2 on Study Day 156, to grade 1 on Study Day 218, and was resolved with normal LFTs on Study Day 252. The Investigator, Applicant, and FDA agreed that DILI was related to ribociclib. This case satisfied clinical Hy's Law criteria.

Participant ID# (b) (6) is a 61-year-old female with PMH of Gilbert's syndrome. She was diagnosed with Stage IIIA breast cancer on (b) (6) and treated with neoadjuvant EC-T, mastectomy, ALND, and randomized to receive letrozole + ribociclib. At baseline, her LFTs were normal. On Study Day 42, she had grade 2 ALT, grade 1 AST, and grade 1 total bilirubin with normal alkaline phosphatase and GGT. She had grade 2 asthenia. Ribociclib was interrupted on Study Day 43 and never restarted, and no action was taken with letrozole. On Study Day 56, ALT was grade 3, AST was grade 2, and total bilirubin was grade 2. Between Study Day 62 and 76, AST and ALT were grade 1-2 and total bilirubin was grade 1. On Study Day 96, ALT and AST were grade 2, and total bilirubin was grade 2. Hepatitis A serology was negative. No other serologies or liver biopsy were reported. LFT values continued to fluctuate in the grade 1 and 2 range. As of Study Day 167, ALT was resolved and on Study Day 353, total bilirubin was resolved. Alkaline phosphatase was normal throughout. Another episode of grade 2 bilirubin occurred on Study Day 420 and resolved on Study Day 586. Letrozole was continued throughout, and

ribociclib was never restarted after Study Day 43. The Investigator, Applicant, and FDA agreed that DILI was due to ribociclib, and the case satisfied clinical criteria for Hy's Law.

Participant ID# (b) (6) is a 66-year-old female with no PMH. She was diagnosed with Stage IIA right breast cancer on (b) (6) and treated with lumpectomy, SLNB, breast radiotherapy and was randomized to letrozole + ribociclib. At baseline, her LFTs were normal. On Study Day 43, she had grade 1 ALT and GGT with normal AST, alkaline phosphatase, and total bilirubin. On Study Day 57, she had grade 2 ALT, grade 1 AST and GGT with normal alkaline phosphatase and total bilirubin. No viral serologies or autoimmune hepatitis tests were reported. Ribociclib was permanently discontinued on Study Day 84 (patient's last dose was Study Day 77). On Study Day 85, ALT and ALT worsened to grade 3 with grade 2 GGT and normal alkaline phosphatase and total bilirubin. Letrozole was discontinued on Study Day 92. She was treated with Silybum marianum. On Study Day 93, she had grade 4 ALT, grade 3 AST and GGT, with alkaline phosphatase and total bilirubin not done. On Study Day 127, she still had grade 3 AST and ALT, grade 1 alkaline phosphatase and grade 1 total bilirubin. She was withdrawn from the study by her physician that day with abnormal LFTs ongoing and no further labs available. The Investigator, Applicant, and FDA all agree that DILI was due to ribociclib, though the case did not meet Hy's Law criteria.

Participant ID# (b) (6) is a 43-year-old female with no PMH. She was diagnosed with right-sided Stage IIIA breast cancer on (b) (6), and treated with mastectomy, ALND, and adjuvant TC and randomized to anastrozole + goserelin + ribociclib. At baseline, her LFTs were normal. On Study Day 145, she developed grade 1 AST and ALT and was diagnosed with DILI, grade 2. Her total bilirubin remained normal. On Study Day 225, ribociclib was interrupted (last dose on Study Day 217) and never restarted for grade 1 AST and ALT with grade 1 diarrhea. On Study Day 239, ALT was grade 3 and AST was grade 1. Serologies were performed for viral hepatitis, but no results provided. On Study Day 252, ALT and AST were grade 3. An abdominal ultrasound was performed with results not reported. On Study Day 260, ALT was grade 4, AST was grade 3 and when numbers continued to rise, she was hospitalized on Study Day 316 for DILI. A liver biopsy on Day 317 showed moderate active hepatitis with prominent lobular inflammation and necrosis. Steroids were given. By Study Day 350, AST and ALT were grade 1, and by Study Day 379, they were resolved. The patient subsequently had grade 1 AST on Study Day 407, which resolved on Study Day 421. As of Study Day 504, transaminases and total bilirubin were all normal and remained normal on labs through Study Day 841. The Investigator, Applicant, and FDA all agree that DILI was due to ribociclib, although the case did not meet Hy's Law criteria.

Participant ID# (b) (6) is a 32-year-old female with no PMH. She was diagnosed with Stage IIA breast cancer on (b) (6), and treated with neoadjuvant AC-T, lumpectomy, ALND, and breast radiotherapy then randomized to letrozole and goserelin + ribociclib. At baseline, her LFTs were normal. On Study Day 56, she had grade 1 AST and ALT with normal alkaline phosphatase and total bilirubin. No action was taken. On Study

Day 84, her AST was grade 3, ALT was grade 4, alkaline phosphatase was grade 1, and total bilirubin was normal. Ribociclib was interrupted on Day 85 (last dose was taken on Day 77) and never restarted. On Study Day 90, AST and ALT were grade 4, alkaline phosphatase was grade 1, and total bilirubin was grade 1. Letrozole was interrupted from Study Day 91 to 118. By Study Day 140, AST, ALT, and alkaline phosphatase were grade 1 and total bilirubin was normal, and on Study Day 252, AST and ALT were resolved, total bilirubin was normal, and alkaline phosphatase remained grade 1. These results remained the same through Study Day 1000. No biopsies, viral serologies, or autoimmune testing was reported. The Investigator, Applicant, and FDA all agree DILI was due to ribociclib, and this case satisfied clinical criteria for Hy's Law.

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

The Applicant's Position:

Patient-reported outcomes have been discussed in Section 8.1.2.

The FDA's Assessment:
Refer to the section discussing patient-reported outcomes in Section 8.1.2.

8.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position:

The comprehensive discussion of intrinsic factors by demographic characteristics (sex and menopausal status, age and age categories, race and race categories, ethnicity, American Joint Committee on Cancer (AJCC) Anatomic Stage groups) and by special populations (baseline hepatic function, baseline renal function) in Study O12301C is described based on the primary iDFS analysis data cut-off.

No clinically relevant differences were observed by group for TEAEs, AESI groupings, and/or on-treatment deaths, except for the following intrinsic factors:

Adverse events by sex and menopausal status
No trends in TEAEs by SOC were observed by menopausal status. When considering male patients, overall trends in TEAE data were no different; albeit the number of male patients was few. In the ribociclib + ET group, events belonging to the Renal toxicity AESI were numerically lower in premenopausal women (2.8%), compared with postmenopausal women (7.9%). This pattern was also observed in the ET only group (0.8% and 2.9%, respectively). Of note, there were fewer premenopausal women (0.2%) who presented AKI, compared with postmenopausal women (0.4%). This pattern was observed in the ET only group (0 vs. 0.2%, respectively). No other trends in AESI by menopausal status were observed.
For male patients only, no trends in AESI groupings by sex were observed. However, as the number of male patients was low, i.e. 19 patients, these data should be interpreted with caution. No male patient presented AKI. In the ribociclib + ET group, on-treatment deaths were 0.5% in

premenopausal women, compared with 0.7% in postmenopausal women. This pattern was also observed in the ET only group (0.2% and 0.5%, respectively). There was 1 premenopausal woman (0.1%) who died due to COVID-19 pneumonia, compared with 5 postmenopausal women with COVID-19 events. This pattern was not observed in the ET only group. There was 1 on-treatment death due to AE (road traffic accident) in male patients (ribociclib + ET: 10.0%) [SCS Study O12301C-Section 5].

Adverse events by age

In general, no trends in TEAEs as SOCs by age, i.e., younger than 45 years, ≥ 45 years to 54 years, ≥ 55 years to 64 years vs. the older subgroup, were observed. When assessing these data as the elderly subgroup, blood and lymphatic system disorders SOC was more frequent overall and in the ribociclib + ET group (57.1% and 11.1%, respectively), compared with patients younger than 75 years (47.0% and 8.5%). No trends in TEAEs by SOC were observed when patients were younger than median age vs. median age and older. Of note, median age was 52.0 years of age.

No trends in AESI by age, younger than 65 years vs. the older subgroup, were observed. When assessing these data as the elderly subgroup, Anemia AESI was more frequent overall and in the ribociclib + ET group (25.0% and 7.9%, respectively), compared with patients younger than 75 years (7.9% and 2.9%, respectively). In general, overall Renal toxicity AESI was more frequent in elderly patients irrespective of study treatment (12.5% vs. 11.1%), but more frequent in patients younger than 75 years in the ribociclib + ET group (5.6% vs. 1.8%).

There was no trend in on-treatment deaths in patients 65 years of age and younger (0.5%), compared with the older subgroup (0.8%). When assessing these data by primary reason for death, there was no trend. There was no on-treatment death in the elderly. On-treatment deaths when primary reason was AE in patients younger than the median age was 0.1% vs. those who were ≥ median age at 0.4%. In the ribociclib + ET group, patients who were younger than the median age had on-treatment deaths due to AE at 0.2% vs. those who were ≥ median age at 0.5%. The most frequent of these belonged to infections and infestations SOC (younger than median age, 0.1%; older than median age, 0.4%) and were COVID-19 events [SCS Study O12301C-Section 5].

Adverse events by race

Overall, events related to ET presented less frequently in patients who were Asian (51.8% vs. 57.5%), compared to not Asian (64.2% vs. 62.1%). Several categories of TEAEs presented more frequently in patients who were Asian vs. not Asian. These were grade ≥ 3 AEs, leading to dose reduction, interruption, and those requiring additional therapy (Asian: 76.5%, 29.7%, 86.2%, 85.0%, respectively; not Asian: 60.3%, 18.7%, 70.3%, 74.5%, respectively) in the ribociclib + ET group. However, this trend was not observed in the ET only group (Asian: 13.7%, NA, 5.1%, 70.3%, respectively; Not Asian: 18.5%, NA, 7.5%, 63.0%, respectively).

Trends were observed of less frequent TEAEs of several SOCs (blood and lymphatic system disorders; general disorders and administration site conditions; hepatobiliary disorders;

musculoskeletal and connective tissue disorders; reproductive system and breast disorders; vascular disorders) in Asian patients (27.1%, 42.1%, 1.8%, 48.8%, 6.2%, 19.7%), compared to not Asian (49.5%, 53.0%, 5.2%, 60.0%, 13.8%, 32.5%) in the ribociclib + ET group. However, this trend was only observed when events belonging to the blood and lymphatic system disorders; and general disorders and administration site conditions in patients in the ET only group (Asian: 2.9%, 23.0%, respectively; not Asian: 9.5%, 36.1%, respectively).

Conversely, there were more frequent TEAEs within 1 SOC (investigations) in Asian patients (all grades, 82.4%; grade-3, 48.8%; grade-4, 2.9%), compared to combining patients into the category of not Asian (all grades: 61.2%; grade-3, 19.3%; grade-4, 2.1%) in the ribociclib + ET group. The trend was not observed when events belonged to investigations in the ET only group (Asian: all grades, 34.8%; grade-3, 1.9%; grade-4, 0.3% and not Asian: all grades, 30.4%; grade-3, 2.4%; grade-4, 0.3%) [SCS Study O12301C-Section 5].

Overall, events in the Neutropenia AESI were more frequent in Asian patients (79.1% vs. 6.4%) and predominantly decreased neutrophil count, compared to not Asian (59.4% vs. 4.3%). Events belonging to the Reproductive toxicity AESI were only mastitis (0.6% vs. 0.3%) in Asian patients. This pattern was not observed in patients not Asian. For some races, the number of patients was low and data should be interpreted with caution. When patients were American Indian or Alaskan native (n=7), Infections AESI was highest (100% vs. 66.7%): 5 of these 7 patients had COVID-19, grade 1 / 2. Similarly in Black or African American patients (n=84), events in the Infections AESI (48.8% vs. 23.3%) were most frequently COVID-19 (14.6% vs. 9.3%). In general, trends in on-treatment deaths by race were not observed. There was no on-treatment death due to AE in American Indian or Alaskan native or Asian patients. There was no on-treatment death due to AE in Black or African American patients. All remaining on-treatment deaths due to AE were White patients (overall: 0.4%; 0.5% vs. 0.2%).

The primary reason for all on-treatment deaths in Asian patients (overall: 0.5%) was disease recurrence (0.3% vs. 0.6%). Conversely, on-treatment deaths due to disease recurrence included not Asian patients (overall: 0.2%), but also were due to AE (overall: 0.3%) irrespective of treatment group (0.5% vs. 0.2%) [SCS Study O12301C-Section 5].

Adverse events by ethnicity

Events in the skin and subcutaneous tissues disorders SOC were more frequent in patients with unknown ethnicity (43.9%), compared with the other 2 ethnic categories (Hispanic/Latino: 28.0%; non-Hispanic/non-Latino: 36.4%) in the ribociclib + ET group. However, this pattern was not observed in the ET only group (15.2%, 18.9%, 25.0%, respectively). No other trends by ethnicity were observed. No trends in AESI by ethnicity were observed. There was 1 patient (0.2%) with on-treatment death (disease recurrence) whose ethnicity was Hispanic/Latino. In non-Hispanic/non-Latino patients, on-treatment deaths due to AE (0.5% vs. 0.2%) were generally comparable to on-treatment deaths due to disease recurrence (0.3% vs. 0.2%). There was 0 on-treatment deaths in patients of unknown ethnicity [SCS Study O12301C-Section 5] [SCS Study O12301C-Section 5].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment regarding AEs by age, race, and ethnicity with the following important caveat. As noted in Sections 8.2 and 8.2.2, the study population, which was three-quarters white or Caucasian, was less diverse than the US population. This limits the ability to draw conclusions about differences in efficacy or safety/tolerability by race or ethnicity. Black or African-American patients in particular were markedly under-represented in the NATALEE trial. Diversity plans did not exist at the time the NATALEE study was designed. As a postmarketing commitment, FDA will ask the Applicant to conduct an integrated analysis from ongoing, completed, or planned (e.g., CLEE011O12301C/NATALEE/NCT03701334 and adjuvant WIDER/NCT05827081) clinical trials and other potential data sources as appropriate, enrolling sufficient representation of racial and ethnic minority patients to reflect the U.S. population of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative early breast cancer, and submit these data to further characterize the efficacy and safety of the addition of ribociclib to an AI in the adjuvant setting in these patient subgroups. This PMC is discussed in further detail in Section 13.

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Evaluation of the data from Study O12301C showed no imbalance in the incidence of SPM events between the two treatment arms.

Comprehensive evaluation of second primary malignancies (SPM) with ribociclib is provided in [Benefit:Risk assessment based on (b) (4) presence in Kisqali] included in this submission.

The FDA's Assessment:

FDA analyzed secondary malignancies and generally agrees with the Applicant's assessment that there does not appear to be an increased incidence of second primary malignancies with ribociclib use based on results of the NATALEE trial at this time. This is discussed in further detail below. The following important background information relates to the potential risk of second primary malignancy with ribociclib.

(b) (4) is a nitrosamine drug substance-related impurity (NDSRI) found in ribociclib succinate drug substance as well as the drug product. Using the Carcinogenic

Potency Categorization Approach, (b) (4) is potency category 3 with a recommended acceptable intake limit of (b) (4) ng/day per FDA Guidance. The impurity level found in ribociclib tablets used in the NATALEE trial exceeded the level recommended by ICH S9 for people with early-stage cancer.

On March 6, 2024, FDA placed all early breast cancer trials of ribociclib under IND 117796 on partial clinical hold, including the NATALEE trial. Deficiencies included insufficient information to assess risks to human subjects based on the available mutagenicity data and insufficient information in the Investigator's Brochure (IB) on the potential harms of the observed (b) (4) levels. The Applicant was required to issue a Dear Investigator Letter, reconsent all patients receiving ribociclib for early breast cancer, and update the IB to remedy these deficiencies.

The Applicant conducted *in vitro* and *in vivo* tests to evaluate the mutagenicity and genotoxicity of (b) (4). The Applicant performed an Enhanced Ames Test (EAT), which did not show (b) (4) to be mutagenic.

The Applicant conducted an *in vivo* transgenic gene mutation assay in the Muta™Mice to evaluate the genotoxic potential of (b) (4) in bone marrow, liver, kidney, and the duodenum per the OECD 488 guideline. (b) (4) was administered at doses of 100 mg/kg/day to female mice and 25, 50, or 100/80 mg/kg/day to male mice. On April 8, 2024, the Applicant notified the FDA of initial results of the *in vivo* Muta™Mice mutagenicity study which found statistically significant increases in mutant frequency across all dose levels in the duodenum in male mice administered (b) (4) when compared to control animals. On April 26, 2024, the Applicant notified the FDA of updated results of the *in vivo* Muta™Mice mutagenicity study, which found statistically significant increases in mutant frequency across all dose levels in the liver and duodenum of both male and female mice administered (b) (4) compared to control animals.

FDA had a Type A CMC meeting with the Applicant on May 13, 2024 to discuss proposed manufacturing changes to limit the maximum intake of (b) (4) associated with ribociclib to (b) (4) ng/day, corresponding to a maximum of (b) (4) ppm intake. Between May and September 2024, the Applicant updated the manufacturing process for ribociclib to decrease the (b) (4) impurity level to fall within the acceptable intake limit, implemented refrigeration of (b) (4) the drug product prior to dispensing to patients, and decreased storage shelf-life to 12 months. During the review of the sNDA, the Applicant provided additional stability data to support the proposed control strategy for (b) (4). With these updated manufacturing processes, the Applicant now proposes (b) (4) uptake with ribociclib not to exceed (b) (4) ng/day for all patients with breast cancer, including for patients with advanced or metastatic breast cancer. (b) (4).

Per the Applicant, (b) (4)

With these manufacturing changes, the (b) (4) impurity is now within FDA's recommended limits for nitrosamine impurities, and thus it should not pose a risk for secondary malignancy in patients treated in the postmarket setting.

Given that the risk of recurrence from high-risk stage II and III breast cancer, which is often distant and incurable, exceeds the potential risk of future secondary malignancy, the review team concluded that the benefit-risk was acceptable both to continue the NATALEE trial with appropriate informed consent and to support regulatory approval of ribociclib for this population.

As of the 90-day safety update, the number of all-grade second primary malignancies (1.9% on ribociclib + ET vs 2.2% on ET only), grade ≥3 second primaries (1.2% on ribociclib + ET vs 1.3% on ET only), and deaths due to second primary (0% in both arms) were similar between treatment groups. Thus, there was no apparent increase in the incidence of second primary malignancies in patients who received ribociclib in the NATALEE trial, with the caveat that follow-up is limited at this time, and malignancies related to nitrosamine impurities may take as long as decades to manifest. There was also generally no pattern to the secondary malignancies that were reported in the NATALEE trial, with most tumor types occurring in a single patient. Exceptions that were more common in those who received ribociclib included melanoma, which occurred in 3 (0.1%) of patients in the ribociclib + ET arm and 0 patients in the ET alone arm, and papillary thyroid cancers, which occurred in 5 (0.2%) of the ribociclib + ET arm and 2 (0.1%) of the ET alone arm. Interestingly, there were fewer cases of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) in the ribociclib + ET arm than in the control arm. This is unexplained as baseline chemotherapy and disease characteristics were well-balanced between the two treatment arms on NATALEE.

Human Reproduction and Pregnancy

The Applicant's Position:

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman.

In Study O12301C, female patients who did not meet the status of postmenopausal were considered WOCBP and were required to have a negative pregnancy test to qualify for study entry. Further, WOCBP had to be willing to use highly effective contraception per protocol.

There was one pregnancy reported in 1 patient (< 0.1%) who was randomized to the ribociclib + ET treatment arm based on the FAS. This patient with a positive screening test was discontinued prior to starting study treatment. Another patient who did use contraception (contraceptive implant) with no failure was reported with pregnancy. This WOCBP female patient was randomized to ribociclib + ET. The known dosing windows were as follows: ribociclib 400 mg, (b) (6); letrozole, (b) (6); and goserelin, (b) (6). It was the patient's decision to discontinue all treatments. EOT serum pregnancy test was negative on (b) (6). Impregnation date was unknown. During a follow-up visit (b) (6), this patient was 4 months pregnant, which is more than 30 days

after the last dose of ribociclib, letrozole, and goserelin. On (b) (6), an ultrasound T2 scan was normal. There were no infections during the pregnancy. Neonate delivery date was (b) (6). The known safety information is as of (b) (6) (MfCtrNo NVSC2022FR246991). As part of current good pharmacovigilance practices (GVP), Novartis performs due diligence as follow-up and will continue to collect additional information on the neonate case [SCS Study O12301-Section 5.3]

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. The Applicant's proposed indication includes pre- and perimenopausal females. Because ribociclib is to be co-administered with an AI, and AIs are not efficacious in the setting of functioning ovaries, all females who are not in confirmed menopause require concurrent ovarian suppression, which is clinician-administered in a health care setting. The USPI reflects this, and the need for concurrent ovarian suppression is well-known to US oncologists, thus the rate of pregnancy is expected to be low; however, clinicians should emphasize that adequate contraception is required with ribociclib use for those of childbearing potential. The risk of fetal harm to humans exposed to ribociclib in pregnancy is poorly characterized.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Refer to Section 10.

The FDA's Assessment:

The NATALEE trial was limited to adults age ≥18 and thus provides no new information regarding pediatrics and assessment of effects on growth. The status of agreed iPSP is summarized in Section 10.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose: No new information about overdose has been generated in support of this dossier; recommendations are described in the approved prescribing information.

In Study O12301C, a grade-3 SAE of overdose was reported in 1 patient (< 0.1%) who received ribociclib + ET. This elderly patient took 3 tablets of ribociclib daily from Day 1 to Day 21, which was 600 mg instead of 400 mg, as per protocol. Concomitant AE at the time was grade 1 tremor. The last dose of 600 mg was taken on Day 21 and then 1 week off drug (second cycle was delayed due to the neutropenia). Ribociclib was interrupted on Day 28 to Day 34 due to grade 3 neutropenia (onset: Day 13). The patient recovered on Day 34 and 400 mg ribociclib dosing was restarted the next day. The patient was re-educated on the proper dosing regimen.

Drug abuse: No new information about abuse/dependence potential has been generated in support of this dossier. There is no known potential for abuse of ribociclib and no abuse studies have been performed.

Withdrawal and rebound: No new information about withdrawal and rebound has been generated in support of this dossier. No studies have been conducted to assess withdrawal and rebound effects. Based on the product profile, no withdrawal effect is expected [SCS Study O12301C-Section 5.4 to 5.6].

The FDA's Assessment:

FDA concurs that the current submission provides limited information regarding "overdose" and no new information regarding withdrawal or rebound. The review team noted that 245 (10%) of patients on the ribociclib + ET arm had a protocol deviation related to dosing. In NATALEE, a protocol deviation related to dosing was defined as any of the following: a participant did not adhere or exceeded the prescribed daily dose of ribociclib for >3 days, or exceeded the planned duration of ribociclib for >3 days, or received a single dose of ribociclib ≥900 mg, or had an off- period of <7 days in a cycle. The most common dosing protocol deviation was exceeding the planned duration of ribociclib. The mean number of extra days on ribociclib was 2.7 days. In response to an information request from the Agency, the Applicant submitted an analysis demonstrating that the incidence and severity of AEs in participants with dosing-related protocol deviations were similar to that in the overall safety population. In particular, the incidence of grade ≥3 AEs (62.4% vs 62.6%, respectively) and the incidence of AESIs were not significantly increased.

The Applicant was queried about the reasons for the frequency of observed dosing-related protocol deviations on the NATALEE trial, to determine whether the USPI should be modified to provide clearer instructions on dosing in the postmarket setting. Per the Applicant, on study, dosing instructions was provided to all participants, and all were issued a medication diary to be completed for each visit by both the patient and study site staff. Patients were instructed to return the diary as well as unused medication at each visit for assessment of compliance by study staff. A drug accountability log was maintained and reviewed by the trial monitor at site visits and study completion. There was no systematic capture of details regarding the reasons for dosing-related protocol deviations, and thus the reason for the dosing errors remains uncertain. It is possible that these errors will be more common in the postmarket setting where medication diaries are seldom used, and compliance is rarely formally assessed. Given that the drug is usually dispensed monthly in clinical practice, however, the harm of likely potential dosing errors by the patient is expected to be limited.

The highest dose of ribociclib to which a patient is reported to have been exposed in NATALEE was 600 mg/day, which was an error on the patient's part, and was corrected back to the prescribed dose of 400 mg/day. As 600 mg/day is the approved dose in combination with ET in the metastatic setting, this does not provide any new information regarding "overdose."

The lower dose of ribociclib (400 mg/day) used in the NATALEE trial and being approved in the adjuvant setting provides a margin of safety to patients with early breast cancer who may inadvertently exceed the intended adjuvant daily dose or number of days of treatment per cycle.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Routine signal detection activities included regular review by qualified medical personnel of worldwide literature searches, frequency analyses in external and internal safety databases, registries containing safety data, blinded review of safety data reported from ongoing clinical studies, as well as postmarketing reports in the Novartis Safety Database.

Cumulatively, since the time of the first marketing authorization approval of Kisqali in 2017, the established comprehensive safety monitoring identified 2 new safety signals (Interstitial Lung Disease/Pneumonitis and Toxic Epidermal Necrolysis) that eventually were added as postmarketing ADRs in the Kisqali prescribing information with appropriate communication within the Warning and precaution section. Considering the implemented risk minimization measures, there was no impact on the individual and the benefit-risk assessment of ribociclib.

With the estimated cumulative exposure of approximately (b) (4) PTY (Kisqali PSUR 13 Mar 2022 to 12 Mar 2023-Section 5.2), the evaluation and detailed analysis of the known ribociclib-associated safety concerns in Kisqali PSURs did not reveal any evidence of increased reporting rates or increased severity of the AEs supporting the adequacy of established risk minimization activities in the currently approved indication. As demonstrated in Kisqali PSUR (Kisqali PSUR 13 Mar 2022 to 12 Mar 2023), based on the cumulative review of available safety data from all sources, the benefit-risk assessment remained favorable and unchanged [SCS Study O12301C-Section 6].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of safety based upon the postmarket experience. The updated USPI accurately characterizes the risks of ribociclib, and the benefit-risk assessment remains favorable for the intended use population. The safety of ribociclib will continue to be monitored in the postmarket setting.

Given the safety signal for ILD identified in the postmarket use of ribociclib in the metastatic setting, there was concern for an increased risk of ILD in the adjuvant setting where most patients with stage II/III breast cancer will receive adjuvant radiotherapy to the breast/chest wall and/or regional lymph nodes. FDA therefore analyzed interstitial lung disease (ILD) in the NATALEE trial as a grouped term (consisting of PT terms of interstitial lung disease, pulmonary fibrosis, pneumonitis, and radiation pneumonitis). There were 30 (1.2%) patients who received ribociclib + ET with an ILD AE compared to 18 (0.7%) of those receiving ET only. All cases were grade 1 or 2 except for one patient

(<0.1%) in the ET only group with grade 3 ILD. Therefore, while there was a 0.5% increase in risk of all-grade ILD with ribociclib in NATALEE, the risk is low overall, and cases do not appear to be more severe with ribociclib use.

Although FDA's analysis of rash as a grouped term identified an increased incidence with ribociclib + ET compared to ET only (13% vs 5%), most of these were grade 1/2. Grade ≥3 rash was rare and equal (0.2%) in both arms. There were no cases of toxic epidermal necrolysis reported with ribociclib in the NATALEE trial.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Overall frequency and severity of AEs, especially dose dependent toxicities, is less in Study O12301C compared with data at the 600 mg dose in the aBC setting. The safety follow-up in Study O12301C in terms of patient-years of exposure was 6904.3 patient-years for the ribociclib + ET group vs. 6487.3 patient-years for the ET only group, or an additional 1018.4 patient-years since IA3. These data show that the level of safety follow-up completed in the study thus far is adequate to detect any signals that are related to the safety profile of ribociclib, including those that are not dose-dependent and/or rare events, and is unlikely to change substantially with longer follow-up.

Furthermore, the long-term safety of ribociclib is well established based on treatment in the advanced/metastatic BC population (1065 patients exposed to ribociclib in the pool of the three pivotal trials in aBC, with an estimated exposure of 2081 PTY [Study A2301 SCS Add.-Table 1-8]) and a higher starting dose of ribociclib (600 mg), with results showing no change to the safety profile of the drug over time compared with the primary analyses. As of 12-Mar-2023, 10,289 subjects/patients have received ribociclib in clinical trials, and the cumulative post-authorization patient exposure since the first launch of ribociclib is estimated to be approximately (b) (4) PTY. Evaluation of the cumulative safety data from clinical trials and post-marketing sources did not reveal any new safety signal related to the long-term use of ribociclib. With longer follow-up and more patients completing ribociclib treatment in the eBC setting, no new safety signals were identified and overall, the safety profile remains unchanged, indicating stability of safety findings [CO Study O12301-Section 6.3.1]. Therefore, the safety in patients with eBC is not expected to significantly change in post-marketing setting.

The FDA's Assessment:

FDA disagrees with the Applicant's statement that "the safety in patients with eBC is not expected to significantly change in post-marketing setting." Granting an indication in early breast cancer results in both a marked increase in the number of patients eligible to receive treatment, as well as a heightened scrutiny and level of concern for AEs given that many patients, even those at high risk, may be cured by existing local and systemic adjuvant therapy. In addition, despite modernized eligibility criteria, clinical trials enroll a population with more favorable performance status and fewer comorbidities/concomitant medications compared to the general population. We therefore cannot conclude that the

safety in patients with eBC will not change in the postmarket setting when a much larger and more diverse group of patients will be exposed to ribociclib. The Applicant and the FDA will continue to monitor safety in the postmarket setting and update the USPI as needed.

As noted, there was an increased risk for overall and severe COVID-19 in patients who received ribociclib, although this risk diminished over the course of the study. This will also continue to be monitored in the postmarket setting.

8.2.11 Integrated Assessment of Safety

Data:

Table 32: Summary of deaths and adverse event categories in Study O12301C (Safety set)

	Final iDFS analysis: 21-Jul-2023 data cut-off							
	Ribociclib + ET [N=2525]				ET only [N=2442]			
Category	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All deaths[1]	83 (3.3)	NA	NA	NA	89 (3.6)	NA	NA	NA
On-treatment deaths[2]	20 (0.8)	NA	NA	NA	9 (0.4)	NA	NA	NA
AEs	2474 (98.0)	1463 (57.9)	133 (5.3)	11 (0.4)	2145 (87.8)	425 (17.4)	40 (1.6)	4 (0.2)
Suspected to be drug-related	2368 (93.8)	1284 (50.9)	101 (4.0)	1 (< 0.1)	1566 (64.1)	97 (4.0)	6 (0.2)	0
SAEs	357 (14.1)	252 (10.0)	44 (1.7)	11 (0.4)	256 (10.5)	192 (7.9)	26 (1.1)	4 (0.2)
Suspected to be drug-related	68 (2.7)	39 (1.5)	17 (0.7)	1 (< 0.1)	13 (0.5)	9 (0.4)	0	0
AEs leading to discontinuation	524 (20.8)	201 (8.0)	36 (1.4)	2 (0.1)	134 (5.5)	38 (1.6)	5 (0.2)	3 (0.1)
Suspected to be drug-related	435 (17.2)	165 (6.5)	26 (1.0)	0	94 (3.8)	18 (0.7)	0	0
AEs requiring dose interruption	1858 (73.6)	1226 (48.6)	87 (3.4)	0	199 (8.1)	67 (2.7)	8 (0.3)	0
Suspected to be drug-related	1635 (64.8)	1156 (45.8)	70 (2.8)	0	99 (4.1)	27 (1.1)	3 (0.1)	0
AEs requiring dose adjustment	586 (23.2)	338 (13.4)	36 (1.4)	0	NA	NA	NA	NA
Suspected to be drug-related	561 (22.2)	330 (13.1)	36 (1.4)	0	NA	NA	NA	NA
AEs requiring additional therapy	1962 (77.7)	499 (19.8)	61 (2.4)	2 (0.1)	1627 (66.6)	297 (12.2)	28 (1.1)	1 (< 0.1)
Suspected to be drug-related	1225 (48.5)	240 (9.5)	32 (1.3)	0	696 (28.5)	58 (2.4)	3 (0.1)	0
AEs of special interest	2183 (86.5)	1291 (51.1)	114 (4.5)	7 (0.3)	1179 (48.3)	168 (6.9)	15 (0.6)	2 (0.1)

	Final iDFS analysis: 21-Jul-2023 data cut-off							
	Ribociclib + ET [N=2525]				ET only [N=2442]			
Category	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Suspected to be drug-related	1886 (74.7)	1188 (47.0)	100 (4.0)	0	203 (8.3)	17 (0.7)	2 (0.1)	0

[1] All deaths including those not considered on-treatment deaths. Includes deaths with cause other than AE. Deaths due to disease progression or other are listed in the All Grades column.
[2] On treatment deaths are defined as occurring on or after treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation.
Includes deaths with cause other than AE. Deaths due to disease progression or other are listed in the All Grades co lumn. Suspected to be drug related refers to any component of study treatment. Additional therapy includes all non-drug therapy and concomitant medications. Discontinuation refers to discontinuation of any treatment component. n=number of patients. Patients are counted once per category at worst toxicity grade in the main category rows, and once per category per toxicity in the related rows.

Source: SCS Add. Study O12301-Table 2-1

The Applicant's Position:

A predictable and manageable safety profile was observed with ribociclib in the eBC setting at the 400 mg starting dose in combination with standard of care NSAI/AI. No new safety signals or safety concerns were identified based on the thorough review of the safety data from Study O12301C. Ribociclib-related AEs are well characterized and are readily identifiable with routine laboratory work or physical examination, are manageable with appropriate intervention (standard medical care and/or through the use of ribociclib dose reduction, temporary treatment interruption or permanent discontinuation), and are generally reversible upon treatment adjustment. The majority of ribociclib discontinuations due to AEs occurred early on in the course of treatment, indicating that if patients tolerate the first few months of treatment, they are likely to tolerate for the duration of the treatment. With the lower starting dose of ribociclib at 400 mg, a lower overall incidence and severity of toxicities was observed compared with that observed at 600 mg in the aBC setting; this is specifically relevant for dose-dependent toxicities including QT interval prolongation and neutropenia.

On-treatment death was reported for 20 patients (0.8%) in the ribociclib + ET group vs. 9 patients (0.4%) in the ET only group within 36 months of treatment plus 30 days of safety follow-up. The main causes of on-treatment deaths in the ribociclib + ET group and ET only group, respectively, were disease recurrence/progression: 9 patients (0.4%) vs. 4 patients (0.2%); and deaths due to COVID-19: 6 patients (0.2%) vs. 1 patient (< 0.1%). Of the 20 total patients who died in the ribociclib + ET group, 8 died within the defined on-treatment period, but >30 days after ending treatment with ribociclib [CO Study O12301-Section 5.7].

Key safety topics

Neutropenia, hepatobiliary toxicity, and QT interval prolongation are known safety concerns that continue to be considered as important identified risks for ribociclib. All appear to be

manageable with appropriate monitoring, and reversible upon recommended dose modification guidance for ribociclib. Although these remain important identified risks for ribociclib, the frequency and severity of neutropenia and QT prolongation events and severity of hepatobiliary toxicity events is lower with ribociclib 400 mg in the eBC setting compared with ribociclib 600 mg in the aBC setting. The data at the final iDFS analysis support previous observations that these events happen early on treatment with ribociclib and their incidence does not increase over time.

Neutropenia

Neutropenia was the most common AE leading to study treatment dose adjustment or dose interruption in the ribociclib + ET group (reported for 12.6% and 42.8% of patients based on the AESI pooled event category). However, neutropenia AESIs leading to discontinuation were infrequent (1.3%; 32 patients) in the ribociclib + ET group. Neutropenia events were generally observed early over the course of treatment with ribociclib, with a median time of 1.0 month to first occurrence of grade ≥3 neutropenia and estimated median duration of grade ≥ 3 neutropenia (that recovered to grade ≤ 2) of 0.3 months in the ribociclib + ET group.

The incidence of grade ≥ 3 neutropenia in Study O12301C (based on the AESI pooled event category) was 43.8% in the ribociclib + ET group (vs. 0.8% in the ET only group). Although there was a high incidence of grade ≥ 3 neutropenia, it did not translate into a clinically significant increase in risk of severe infections in patients treated with ribociclib. Febrile neutropenia events were reported uncommonly, with only two patients discontinuing study treatment due to febrile neutropenia; there were no fatal neutropenia events in either group.

As expected, due to the concentration-dependent effect of ribociclib on ANC level, the incidence of grade ≥3 neutropenia in Study O12301C (43.8%; AESI grouping) with ribociclib 400 mg is lower than the incidence of grade 3/4 neutropenia (62.5%; AESI grouping) for pooled data from Studies A2301, E2301 (NSAI/AI subgroup), and F2301 in advanced/metastatic breast cancer with ribociclib 600 mg.

Management guidelines for neutropenia remain the same as in the approved label for patients with aBC.

QTc interval prolongation

Based on the totality of data, the overall low incidence and types of QT interval prolongation AESI, the change from baseline in QTcF interval, and notable ECG values had a limited impact on patients in Study O12301C. In Study O12301C, the risk difference between the ribociclib + ET and ET only groups for QT prolongation (AESI) grade ≥3 events was 0.5% (95% CI: 0.0, 0.9).

Electrocardiogram QT prolongation events (PT) occurred predominantly within the initial 2 cycles of treatment with ribociclib with the majority events detected around the middle of the first cycle, when the drug is expected to reach its steady state. Of note, no first occurrences of notable QTcF values (> 480 ms) were observed at the beginning of the second cycle of treatment after the scheduled 7-day washout period. No associated cardiac signs or symptoms were

observed at the time of QT prolongation events. Overall, events within the QT prolongation AESI were uncommon and with limited clinical impact rarely requiring dose adjustment, interruption, or discontinuation (0.1%; 0.8%; 0.2% respectively) in the ribociclib + ET group. As expected with the lower starting dose of ribociclib 400 mg in combination with ET in patients with eBC in Study O12301C, less overall incidence of QT prolongation events and considerably lower incidence of notable ECG values were observed compared to that with ribociclib 600 mg in aBC (pooled dataset).

As a result of the evaluation of the safety data related to the QT interval prolongation, Novartis is proposing to update the ribociclib label in regard to ECG monitoring recommendations for patients with eBC.

As described above, ECG prolongation events were of low incidence (1.0% grade ≥ 3 QT ECG prolonged AESI; 0.4% QT interval > 480 ms) without associated cardiac signs or symptoms in ribociclib + ET group. The mean QTcF change (ΔQTcF) from baseline was 9.5 ms at Cycle 1 Day 15 2 hours postdose, which corresponds to steady-state ribociclib concentration. The mean change from baseline was 0.5 ms at Cycle 2 Day 1 predose ECG, which corresponds to the lowest ribociclib concentration, as expected, following the 7 days off dose based on the 3-weeks on/1-week off dosing schedule [QT/QTc Safety Analysis Report Study O12301C]. In view of these data from Study O12301C, Novartis proposes ECG monitoring for patients with eBC at baseline before initiating treatment, and approximately Cycle 1 Day 14 (steady-state ribociclib concentration), with additional ECGs as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

Other risk mitigation measures for QT prolongation including dose modification guidance, baseline threshold of QTcF <450 ms, monitoring of electrolytes, and assessment of relevant medical history and concomitant medications are included in the proposed label.

Hepatobiliary toxicity

Hepatobiliary AESIs, which tended to occur early on treatment, were manageable with protocol dose management guidance specific for hepatotoxicity, and reversible upon ribociclib dose modifications. The majority of Hepatobiliary AESI were increased ALT/AST, which were one of the most common grade ≥ 3 AEs in Study O12301C, and the most common reason for treatment discontinuation due to AE. Hepatobiliary toxicity (primarily LFT increases) has been reported during treatment with ribociclib, predominantly within the initial 3 months of treatment, and should be closely monitored.

There was an 8.3% incidence of grade ≥3 Hepatobiliary toxicity AESIs in the ribociclib pus ET group, and with dose interruptions reported in 12.0% of patients, and adjustments reported in 2.5%. A total of 225 patients (8.9%) discontinued treatment due to these events in the ribociclib + ET group. The risk difference between the ribociclib + ET and ET only groups for grade ≥3 AESIs was 6.8% (95% CI: 5.6, 7.9).

Within Hepatobiliary toxicity AESI, DILI was reported for 9 patients (0.4%) and of these, 5 were grade ≥ 3. Of these 8 patients' events resolved as of DCO. There were 8 clinically confirmed

Hy's Law cases, including 4 of the 9 patients with DILI. All 8 patients were in the ribociclib + ET treatment group (n=2524). Importantly, most (6 out of 8 patients) completely recovered after discontinuation of ribociclib, and two patients were recovering as of the DCO.

Of note, there were fewer grade ≥ 3 hepatobiliary toxicity AESIs for Study O12301C compared with the pooled dataset in the aBC setting at 600 mg [CO Study O12301-Section 6.3.1].

Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. Management guidelines remain the same as in the approved label for patients with aBC.

Subpopulations

No additional safety concerns were raised; subgroup analyses typically demonstrated patterns of events consistent with those reported for the overall population.

The FDA's Assessment:

FDA generally agrees with the Applicant's Integrated Assessment of Safety. Many ribociclib AEs are known to be concentration-dependent, and the lower dose of ribociclib used in NATALEE (400 mg/day) compared with that approved in the metastatic setting (600 mg/day) generally resulted in decreased incidence and severity of AEs in the adjuvant setting, including AESIs.

Addition of ribociclib to ET nonetheless resulted in increased toxicity, including high-grade toxicity, compared to ET alone. Patients receiving ribociclib were more likely to experience a grade ≥3 AE (63.6% vs 19.2%) and more likely to experience a grade ≥3 SAE (12.1% vs 9.2%). On-treatment deaths, defined as deaths while on or within 30 days of the last dose of ribociclib, were uncommon and evenly divided between disease progressions/recurrences and AEs. While deaths during the on-treatment period were increased in the ribociclib + ET group (n=20, 0.8%) compared to those who received ET only (n=9, 0.4%) with COVID-19/COVID-19 pneumonia the most common causes of on-treatment death, deaths overall on study were numerically lower in the ribociclib + ET group. This reflects a decrease in deaths due to disease recurrence, as well as due to COVID-19, over time. As of the 90-day safety update, 4.1% of patients on the ET only arm had died compared to 3.6% on the ET + ribociclib arm. The OS HR was <1. There were no additional on-treatment deaths reported at the 90-day safety update.

Despite the lower dose of 400 mg/day used in this adjuvant trial, toxicity-related treatment interruptions were much more common in patients on ribociclib + ET (73.8% vs 8.1% on ET only), most often due to laboratory abnormalities, and nearly one-quarter of patients (23.8%) required ribociclib dose reduction to 200 mg/day. While many AEs were successfully managed with a combination of treatment interruptions and dose reductions, patients on ribociclib were also more likely to discontinue due to an AE (20.8% vs 5.5%), with nearly one in five patients ultimately discontinuing the CDK 4/6 inhibitor due to a laboratory abnormality or AE.

Adverse events associated with ribociclib were most often related to abnormal laboratory findings, especially neutropenia and elevated transaminases, and were often not associated with symptoms. Most of these occurred in the first few cycles of treatment and improved or resolved with the protocol-specified interruption, dose reduction, or treatment discontinuation as noted above.

The previously identified AESIs of neutropenia, QT prolongation, and hepatotoxicity remain the most prominent safety concerns with ribociclib, although these are less common and less severe than in the prior metastatic trials, likely due to the lower dose of ribociclib used in NATALEE, as well as potentially a healthier adjuvant population. There were no significant increases in neutropenia-associated infections. The incidence and severity of COVID-19 infections were increased with addition of ribociclib, though these did not appear to be associated with treatment-emergent neutropenia. It is possible that the increase in the number and severity of COVID-19 cases may have been related to an increased severity of lymphopenia in patients receiving ribociclib. In particular, there was an increase in the number of on-treatment deaths due to COVID-19, though only one death was reported in a vaccinated patient. This risk of severe COVID-19 appeared to decrease over time on the study, with no COVID-19 deaths reported after early 2022, likely due to the widespread availability of vaccines and COVID-19 therapeutics in the countries where NATALEE was conducted, as well as immunity from prior infections. This AE will continued to be monitored in postmarket safety reporting.

There were no fatal hepatobiliary AESIs, although there were multiple cases of drug-induced liver injury, including cases that met the clinical criteria for Hy's Law. Most of these cases fully resolved with drug discontinuation; the small number of cases of DILI without complete resolution had stable or improving LFTs as of the most recent available information.

There was a small increase in the number of patients with QTc increased >60 ms from baseline or to > 500ms, but the incidence was notably lower than in the metastatic setting, and there were no cases of Torsades de pointes or sudden cardiac death associated with QT prolongation identified on study.

With careful monitoring and treatment interruption, dose reduction to 200 mg/day, or drug discontinuation as described in the updated USPI, the risks of these AESIs can be largely mitigated, and the benefit-risk remains favorable for ribociclib use in the intended population.

There is a potential risk of secondary malignancy related to levels of (b) (4) **, a nitrosamine impurity in the ribociclib supply that was used in the NATALEE trial. Both at the final iDFS analysis and the 90-day safety update, the number of all-grade and grade ≥3 second primary malignancies was comparable in the two arms and there were no deaths in either arm due to secondary malignancy, which is reassuring with the caveat that nitrosamine impurity-related malignancies may take decades to manifest. With manufacturing-related changes, the level of** (b) (4) **in commercially-available**

ribociclib has been adequately controlled to be below the recommended limit for all indications.

At the time of the 90-day safety update, there were no additional on-treatment deaths or new safety signals identified, the HR for OS remained < 1, and the incidence of AESIs was almost identical to that at the time of the final iDFS analysis.

Based on the available safety data, the benefits of ribociclib in iDFS in this population of patients with high-risk Stage II and III HR-positive, HER2-negative early breast cancer outweigh the risks identified in the NATALEE trial. These benefits should not be extrapolated to the broader US population of patients with early-stage HR+, HER- breast cancer, most of whom are at considerably lower risk than patients enrolled to NATALEE. Clinical trials also represent idealized conditions and exclude many patients with comorbid conditions. Therefore, it will be important to continue to monitor this product in adjuvant use in the postmarket setting where safety may differ.

8.3 Statistical Issues

The FDA's Assessment:

There were no major statistical issues with this application. The NATALEE trial met its primary objective of INV-assessed iDFS, showing a statistically significant improvement in iDFS with the treatment of ribociclib + ET compared to ET at IA3. However, at IA3, there was a large amount of censoring for iDFS as only 20% of patients had completed 3 years of adjuvant ribociclib. Thus, there was a concern for a potentially diminishing iDFS effect with longer follow-up, therefore FDA requested that the Applicant continue NATALEE until the final iDFS analysis. At the final iDFS analysis (DCO: July 21, 2023), 43% of patients had completed 3 years of adjuvant ribociclib. The iDFS hazard ratio was 0.75 (95% CI: 0.63, 0.89) which was consistent with the results at IA3. The final iDFS results were also consistent across various sensitivity analyses and exploratory subgroup analyses.

The study was not designed to formally test any secondary endpoints including OS. At the time of final iDFS analysis, the number of deaths observed was less than what was originally projected. Overall, results of OS at the time of final iDFS and at the 90-day safety update support that there appears to be no detriment in OS at this time. A PMC will be issued for the applicant to provide all additional overall survival analyses as prespecified in the protocol and SAP, including OS at the time of end of trial.

8.4 Conclusions and Recommendations

The FDA's Assessment:

Overall the benefit/risk is favorable for ribociclib for the adjuvant treatment of adults with high-risk, stage II and III HR+, HER2-negative breast cancer, based on the results of the NATALEE trial. At the final analysis of iDFS, addition of ribociclib to ET resulted in a 25% relative risk reduction, corresponding to a 3.1% absolute improvement in iDFS. This represents a number needed to treat of 32 to prevent one iDFS event. This magnitude of improvement is considered clinically meaningful as all recurrences result in morbidity, and distant metastatic disease is presently incurable. The majority of deaths, as well as recurrences, due to HR-positive, HER2-negative breast cancer occur in years 5 and beyond. The number of deaths on study was fortunately much lower than projected on both arms, and OS remains immature at this time, but the point estimate for the OS HR is <1.

While patients with both high-risk stage II and III disease were adequately represented in the study to support the indication, only 12% of patients had node-negative tumors. In FDA's analysis, patients with N0 disease had an iDFS HR that was comparable to that of the overall ITT population, and therefore these patients were included in the indication. Importantly, the patients in the NATALEE trial represented a considerably higher risk group than the average US population of adults with HR-positive, HER2-negative breast cancer; <10% had grade 1 tumors, 87% had received prior (neo-)adjuvant chemotherapy, and 88% had N1-N3 disease. The results of the NATALEE trial should therefore not be

extrapolated to the broader US population of patients with HR-positive, HER2-negative breast cancer, most of whom are at much lower risk of recurrence.

The AE profile was similar to that observed in prior trials in the metastatic setting, but the incidence and severity of most AEs was lower, likely due to the lower dose of ribociclib used in the adjuvant setting, as well as a healthier adjuvant population. Neutropenia, hepatotoxicity, and QT prolongation remain the most important identified AESIs with ribociclib. With appropriate monitoring and timely treatment interruption, as well as dose reduction or drug discontinuation for those patients who require it based upon treatment modification guidelines used in the NATALEE trial and reflected in the agreed upon USPI, these risks can be sufficiently mitigated.

There was an increased incidence and severity of COVID-19 infections noted in patients receiving ribociclib, including an increased incidence of on-treatment death due to COVID-19, with deaths confined almost entirely to patients with no prior documented vaccination. The severity of COVID-19 infections appears to have fallen over time; there were no deaths due to COVID-19 reported after early 2022, which likely represents an increasing level of population immunity due to vaccines and prior infections, as well as availability of COVID-19 therapeutics. This safety signal will continue to be monitored in the postmarket setting.

The overall determination of risk-benefit is favorable and supports regular approval.

8.4.1 Approach to Substantial Evidence of Effectiveness

1. Verbatim indication:

209092*: KISQALI is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.*

209935: *KISQALI FEMARA Co-Pack is indicated for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.*

2. SEE was established with
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR
   b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable

a. ☐ SEE was established

b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

x	x
Haley Gittleman, PhD Primary Statistical Reviewer	Joyce Cheng, PhD Statistical Team Lead
x	x
Jennifer Gao, MD Tatiana Prowell, MD Primary Clinical Reviewers	Jennifer Gao, MD Clinical Team Lead

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Not applicable.

10 Pediatrics

The Applicant's Position:
Novartis submitted an iPSP waiver for pediatric studies in eBC to IND 117796 on October 12, 2023, [SN 0974] and a revised version on November 10, 2023. The Agency provided email confirmation on November 17, 2023 that the November 10, 2023 submission of the iPSP waivers for early breast cancer are considered agreed iPSPs.

The FDA's Assessment:

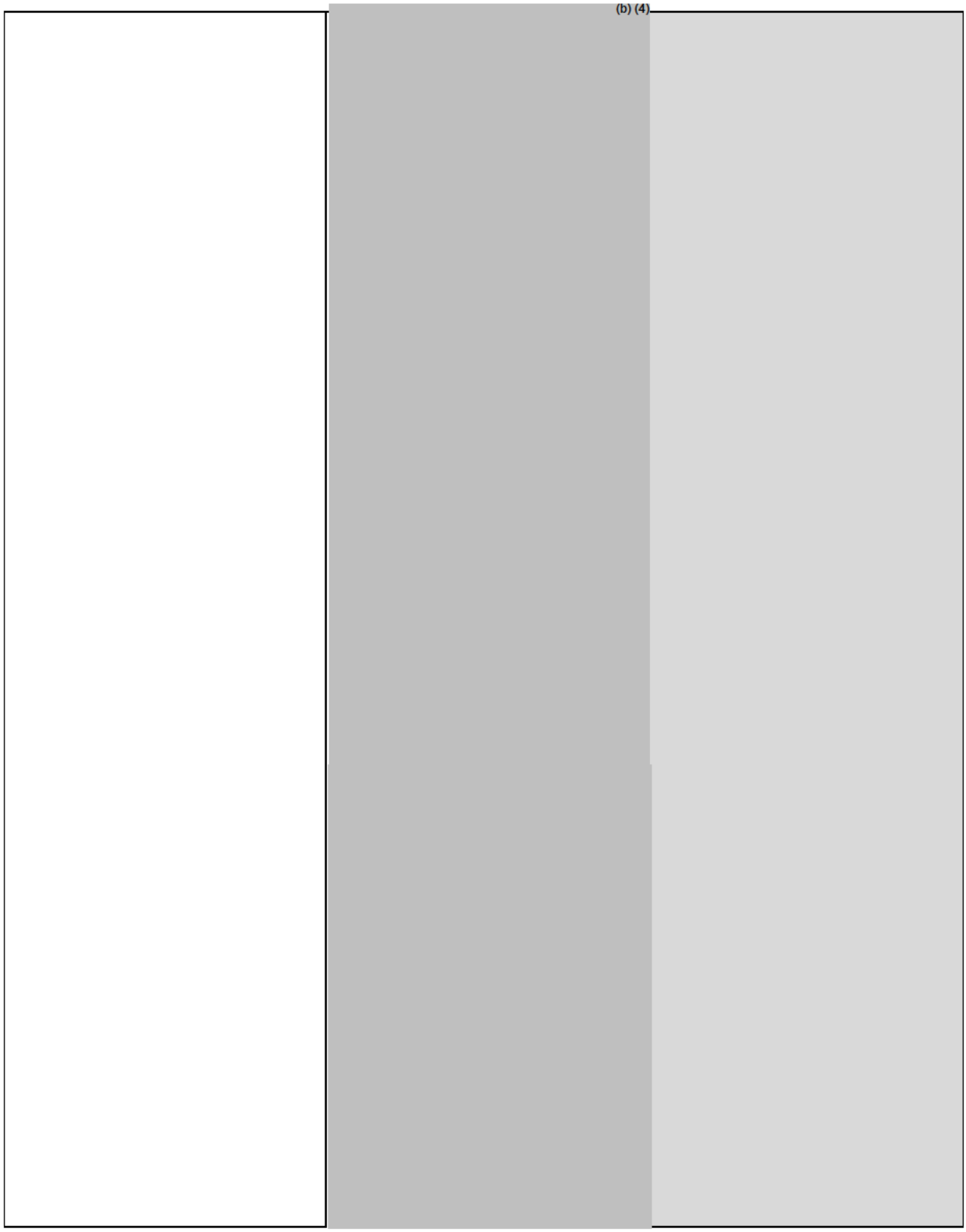
FDA agrees with the Applicant's position.

11 Labeling Recommendations

The Applicant's Position:

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1. Indications and Usage	(b) (4)	FDA recommended indication: 209092: KISQALI is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence. 209935: KISQALI FEMARA CO-PACK is indicated for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.
2. Dosage and administration	(b) (4)	FDA generally agrees with the Applicant's proposed labeling – refer to the USPI for the final agreed upon labeling.
3. Dose modifications		FDA generally agrees with the Applicant's proposed labeling – refer to the USPI for the final agreed upon labeling.

	(b) (4)	
4. Warnings and Precautions		Refer to the USPI for the final agreed upon labeling.



	(b) (4)	
5. Clinical trials experience		Refer to the USPI for the final agreed upon labeling.

	(b) (4)	
6. Drug interactions		Refer to the USPI for the final agreed upon labeling.
7. Use in specific populations (Geriatric use)		Refer to the USPI for the final agreed upon labeling.
8. Clinical pharmacology		Refer to the USPI for the final agreed upon labeling.

	(b) (4)	
9. Clinical studies		Refer to the USPI for the final agreed upon labeling.
10. Patient information		Refer to the USPI for the final agreed upon labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Not applicable.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Postmarketing requirements and commitments were agreed upon with the Applicant, including:

1) PMR: Conduct a carcinogenicity study in mice to evaluate the potential serious risk of carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Draft Protocol Submission:	06/2026
Final Protocol Submission:	11/2026
Study Completion:	12/2028
Final Report Submission:	08/2029

2) PMCs:

a. Conduct an integrated analysis from ongoing, completed, or planned (e.g., CLEE011O12301C/NATALEE/NCT03701334 and adjuvant WIDER/NCT05827081) clinical trials and other potential data sources as appropriate, enrolling sufficient representation of racial and ethnic minority patients to reflect the U.S. population of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative early breast cancer, and further characterize the efficacy and safety of the addition of ribociclib to an aromatase inhibitor in the adjuvant setting in these patient subgroups. This analysis should include, but is not limited to, patients who identify as Black or African-American, and should be reflective of the incidence of early breast cancer in the U.S. in these patient populations. The analyses should support comparable efficacy and safety between the aforementioned populations and White or Caucasian patients.

Draft Protocol Submission (Analysis Plan):	12/2026
Final Protocol Submission (Analysis Plan):	04/2027
Study Completion:	09/2029
Final Report Submission:	03/2030

b. Complete the ongoing clinical trial CLEE011O12301C (NATALEE/NCT03701334) to provide all additional overall survival (OS) analyses as prespecified in the protocol and the statistical analysis plan, including OS at the time of trial completion.

Trial Completion:	06/2026
Final Report Submission:	12/2026

Table 33: FDA – PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
x	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_x_ Yes __ No
x	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _x_ No
x	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x_ No

14 Division Director (DHOT) (NME ONLY)

Not applicable.

X _____

15 Division Director (OCP)

X

Nam Atiqur Rahman, PharmD

16 Division Director (OB)

X

Shenghui Tang, PhD

17 Division Director (Clinical)

X

Laleh Amiri-Kordestani, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

Laleh Amiri-Kordestani, MD

19 Appendices

19.1 References

The Applicant's References:

[Arimidex USPI (2018)] Arimidex (anastrozole) 1 mg tablet - US Prescribing Information (USPI). ANI Pharmaceuticals, Inc. Last updated 13-Dec-2018.

[Aromasin USPI (2021)] Aromasin (exemestane) 25 mg tablet - US Prescribing Information (USPI). Pharmacia & Upjohn Company LLC, New York, NY, USA. Last updated November 2021.

[Bria E, Carlini P, Cuppone F, et al (2010)] Early recurrence risk: aromatase inhibitors versus tamoxifen. Expert Rev Anticancer Ther; 10(8):1239-53.

[Clarke M, Collins R, Darby S, et al (2005)] Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet; 365(9472):1687-717.

[Eggemann H, Ignatov A, Smith BJ, et al (2013)] Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat; 137(2):465-70.

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[Soltamox USPI (2019)] Soltamox (tamoxifen) oral solution - US Prescribing Information (USPI). Midatech Pharma US Inc., Raleigh, NC, USA. Last updated April 2019.

[Verzenio USPI (2023)] Verzenio (abemaciclib) 50/100/150/200 mg film coated tablets. US Prescribing Information (USPI). Lilly USA, LLC, Indianapolis, IN, USA. Last updated March 2023.

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[Zagouri F, Sergentanis TN, Azim HA, et al (2015)] Aromatase inhibitors in male breast cancer: a pooled analysis. Breast Cancer Res Treat; 151:141-7.

The FDA's References:

Not applicable.

19.2 Financial Disclosure

The Applicant's Position:

No clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests are identified on the spreadsheets by bolding the investigators name and are detailed in the disclosure forms that follow FDA Form 3455. These arrangements and interests are provided in Table 34: Summary of disclosable financial arrangements and interests.

Summary of Financial Disclosures from Study CLEE011O12301C

Table 34: Summary of disclosable financial arrangements and interests

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
Dr (b) (6)	2301C	(b) (6)	>$25,000	Meeting and Travel Support
Dr	2301C		>$25,000	Honorarium, Consultant/Advisory Role, Research funding
Dr	2301C		150,000€	Scientific Grant
Dr	2301C		>$25,000	Honorarium, Research Grant
Dr	2301C		>$25,000	Research Grant
Dr	2301C		>$25,000	Consultant
Dr	2301C		>$25,000	Honorarium, Consulting
Dr	2301C		>$25,000	Research Grant

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
Dr (b) (6)	2301C	(b) (6)	>$25,000	Research Grant
Dr	2301C		>$25,000	Honorarium
Dr	2301C		>$25,000	Research Grant
Dr	2301C		>$25,000	Honorarium
Dr	2301C		$28,820	Speaker Grant
Dr	2301C		>$50,000	Equity Ownership
Dr	2301C		>$50,000	Equity Ownership
Dr	2301C		$40,000	Support on electronic platform development
Dr	2301C		$50,000	Project Support

Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis and CRO (TRIO) and multiple investigators used in the study.

Covered Clinical Study (Name and/or Number):* CLEE011O12301C

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4538		
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): 17		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 15 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) NA		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The financial disclosure information was reviewed with no concerns identified.

19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

FDA disagrees that no new information was provided for the sNDA submission. See Section 5 Nonclinical Pharmacology/Toxicology.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1 Population PK Analysis

19.4.1.1 Executive Summary

The FDA's Assessment:

In general, the population PK model adequately characterizes the PK of ribociclib in patients with early breast cancer, and the ribociclib exposure metrics are adequate for use in E-R analyses (e.g., PK-QT analysis).

Physiologically and mechanistically relevant clinical covariates for ribociclib in patients with advanced breast cancer were kept in the model for patients with early breast cancer. No new intrinsic factors were identified for dose adjustment. The recommended dosage for ribociclib in patients with early breast cancer is supported by the population PK analysis results as well as other analyses results (i.e., clinical efficacy, safety, and E-R analyses).

19.4.1.2 PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	• To simulate ribociclib PK in patients in Study O12301C based on the final popPK model and to compare it with the observed PK data. • To generate individual post hoc longitudinal trough concentrations (Ctrough) of ribociclib in patients in Study O12301C to support the exposure-efficacy analysis of Study O12301C. • To provide summary of popPK-predicted PK metrics for patients on 400 mg in Study O12301C to support cross-study comparison (Ctrough, AUC, Cmax on C1D1 and at steady-state) and the PK-QT analysis (Cmax at steady-state).
Study Included	CLEE011O12301C
Dose(s) Included	Ribociclib 400 mg orally QD on Days 1 to 21 of a 28 day cycle (up to 36 months of treatment)

Population Included		PK-iDFS set (N=123) The PK-iDFS set includes all patients in the ER-safety set who had at least one popPK-predicted ribociclib Ctrough, and at least one valid ribociclib PK concentration post-dose.	
Population Characteristics	General	Age median: 55.0 years (range: 30-78 years), 22.0% subjects >=65 years Weight median (range): 68.0 kg (range: 44.5-112.1 kg) 1 (0.8%) male, 122 (99.2%) female 99 (80.5%) non-Asian, 24 (19.5%) Asian	
	Organ Impairment	Not applicable	
	Pediatrics (if any)	Not applicable	
No. of Patients, PK Samples, and BLQ		N=123 patients and 348 evaluable concentrations n (%) of pre-/post-dose: BLQ 2(0.5)	
Sampling Schedule	Rich Sampling	Not applicable	
	In ITT Population	C1D15 at 0, 2, 4 hr were collected.	
Covariates Evaluated	Static	The model included dose as covariates on clearance, inter-compartment clearance, and peripheral volume, and BW on intercompartmental clearance and peripheral volume.	
	Time-varying	Not applicable	
Final Model		**Summary**	**Acceptability [FDA's comments]**
Software and Version		Monolix Suite version 2021R2 utilizing the Novartis DaVinci high	**Acceptable**

	performance computing environment accessed from GPSII. Data preparation, graphical exploration, and other plots were performed using R 4.1.0.	
Model Structure	The ribociclib popPK model developed previously was used to predict PK for patients in Study O12301C to ensure its predictability for these patients. This was a 2-compartmental model structure with delayed zero-order oral absorption and clearance from the central compartment. As patients in the eBC indication showed a higher clearance, the popPK model was updated to account for a lower disease burden in comparison with aBC patients. This updated model was then used to estimate individual PK parameters (CL, V, Q, etc.) for patients in Study O12301C. A reduced model development scheme was applied to update this previous model to describe the PK data in O12301C. The same structure as the previous model was assumed. A base model was defined, where all population parameters were fixed to the previously estimated value. A sensitivity analysis was then performed by estimating one by one all population parameters (including fixed effects, random effect variances and residual variability variances), to identify the closest model which would describe PK in the eBC population.	**Acceptable**

	The predictive performance of the PopPK model was evaluated using a visual predictive check (VPC).	
Model Parameter Estimates	Table 36: Summary of steady-state ribociclib PK parameters across populations and studies	**Acceptable**
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Inter-individual variability was included in the parameter describing the zero-order absorption process (Tk0), along with re-estimation of the clearance parameter. Individual random effects of the parameters were sampled from the normal distributions following the final popPK model estimates for random effects, including both variance and covariance. Estimated residual variability of the final popPK model were included in the simulation as the goal of this step was to reproduce the inter-individual variability of the observed PK data. The updated statistical model did not impacted the overall PK behavior of ribociclib, but allow to address the variability between studies and population.	**Acceptable**
BLQ for Parameter Accuracy	Two patients had only concentrations below the limit of concentration following several days of missed dose and were therefore excluded from the analysis.	**Acceptable**
GOF, VPC	Figure 5	**Acceptable**
Significant Covariates and Clinical Relevance	Not applicable	**The approach is generally acceptable. The**

		impact of intrinsic factors (e.g., age, body weight, sex race, hepatic impairment, renal impairment) on the PK of ribociclib in patients with early breast cancer was similar to that in patients with advanced breast cancer. No new intrinsic factors were identified for dose adjustment.
Analysis Based on Simulation (optional)	Table 37	**Acceptable**
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**
12.3 PK		**In general, the description in section 12.3 of the labeling is acceptable. Edits are added in the final labeling language.**

Table 35: Distribution of intrinsic factors in popPK dataset

Covariate	Category	N
BW#	<50kg	8
	50-60kg	24
	60-70kg	34
	70-80kg	26
	80-90kg	19
	>=90kg	12
Menopausal status	Premenopausal women and men	42
	Postmenopausal women	81
Anatomic stage group	Stage group II	68
	Stage group III	55

#: Subjects with missing records were excluded from the summary.

Source: [SCP Study O12301C-Table 6-1]

Table 36: Summary of steady-state ribociclib PK parameters across populations and studies

Study	Population	Ribociclib Dose (mg)	Dose regimen	Cmax (ng/mL) geo-mean (Geo-CV%)	Tmax (hr) median (min, max)	AUC0-24h (ng·hr/mL) geo-mean (Geo-CV%)	Ctrough (ng/mL) geo-mean (Geo-CV%)	CL/Fss (L/hr) (Geo-CV%)
PopPK simulated data[a]								
Updated O12301C popPK model	eBC	400	Multiple doses (C1D15) with NSAI	952 (39.5)	3.79 (24.4)	10388 (41.0)	263 (52.8)	38.4 (95%CI: 35.5 – 41.9)

Data are presented as geometric mean (CV% geo mean) for all parameters except for Tmax which is presented as median (range).
Formulation of ribociclib used in the studies was capsule unless specified.
[a] population PK parameters are presented as population mean (95%CI)

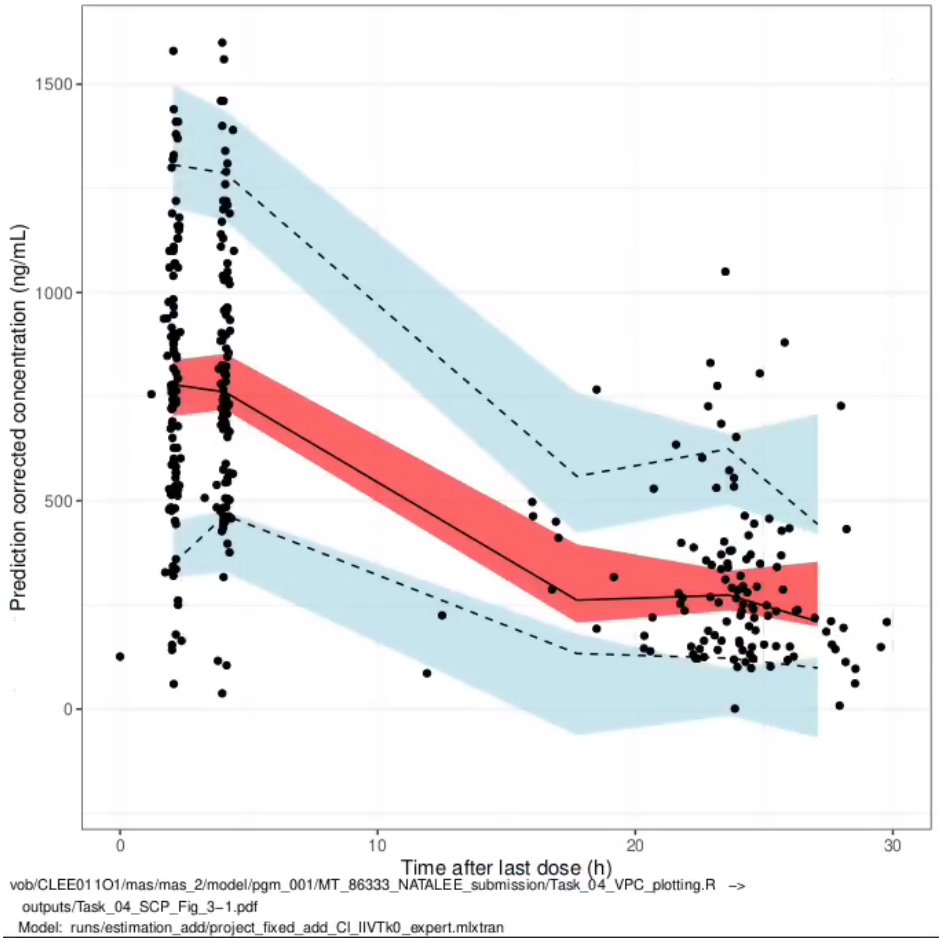
Source: [SCP Study O12301C-Table 3-2]

Table 37: Simulated C1D1 and steady-state ribociclib PK parameters at the dose of 400 mg QD in HR-positive, HER2-negative eBC patients in Study O12301C

Statistic	C1D1	Steady-state
Ctrough (Cmin) (ng/mL)		
Geometric mean (CV%)	108 (50.7)	263 (52.8)
Arithmetic mean (90% CI)	121 (115, 128)	297 (281, 313)
5th percentile (90% CI)	48.9 (48.9, 48.9)	118 (118, 118)
95th percentile (90% CI)	227 (227, 227)	583 (583. 583)
Cmax (ng/mL)		
Geometric mean (CV%)	671 (51.9)	952 (39.5)
Arithmetic mean (90% CI)	751 (705, 796)	1023 (974, 1073)
5th percentile (90% CI)	298 (298, 298)	514 (514, 514)
95th percentile (90% CI)	1423 (1423, 1423)	1767 (1767, 1767)
AUC0-24 (hr·ng/mL)		
Geometric mean (CV%)	5296 (39.5)	10388 (41.0)
Arithmetic mean (90% CI)	5691 (5429, 5953)	11224 (10706, 11724)
5th percentile (90% CI)	2863 (2863, 2863)	5510 (5510, 5510)
95th percentile (90% CI)	9752 (9752, 9752)	19702 (19702, 19702)
Tmax (hr)		
Geometric mean (CV%)	3.79 (24.4)	3.79 (24.4)
Arithmetic mean (90% CI)	3.90 (3.77, 4.04)	3.90 (3.77, 4.04)
5th percentile (90% CI)	2.57 (2.57, 2.57)	2.57 (2.57, 2.57)
95th percentile (90% CI)	5.71 (5.71, 5.71)	5.71 (5.71, 5.71)

Source: [SCP Study O12301C-Table 2-2]

Figure 5: Prediction-corrected visual predictive check (VPC) of the updated popPK model compared with observed PK concentrations in Study O12301C



Dots represent the observed concentrations in the PK-iDFS dataset. Upper and lower borders of the blue area represent the 90% CI of the 5th and 95th percentiles of the simulations, while the red area represents the 90% CI of the median. Similarly, the upper and lower dashed line represent the 5th and 95th percentile of the observations, while the solid line represents the median of the observations.

Source: [SCP Study O12301C-Figure 6-2]

The FDA's Assessment:

The Applicant's population PK analysis is acceptable. Overall, the final population PK model is adequate to characterize the PK profile of ribociclib in patients with early breast cancer as indicated in the Applicant's diagnostic plots. The FDA reviewer repeated and verified the Applicant's analysis with no significant discordance identified. The proposed labeling statements related to PK parameters in Section 12.3 are acceptable.

19.4.1.3 PPK Review Issues

The FDA's Assessment:
No substantive issue.

19.4.1.4 Reviewer's Independent Analysis

The FDA's Assessment:
Reviewer's independent analysis was not performed.

19.4.2 Exposure-Response Analysis

19.4.2.1 ER (efficacy) Executive Summary

The FDA's Assessment:

The E-R analysis for efficacy is considered exploratory due to limited PK data (N=123) collected in study O12301C. The relationship between ribociclib exposure and iDFS cannot be concluded based on the results of E-R analysis.

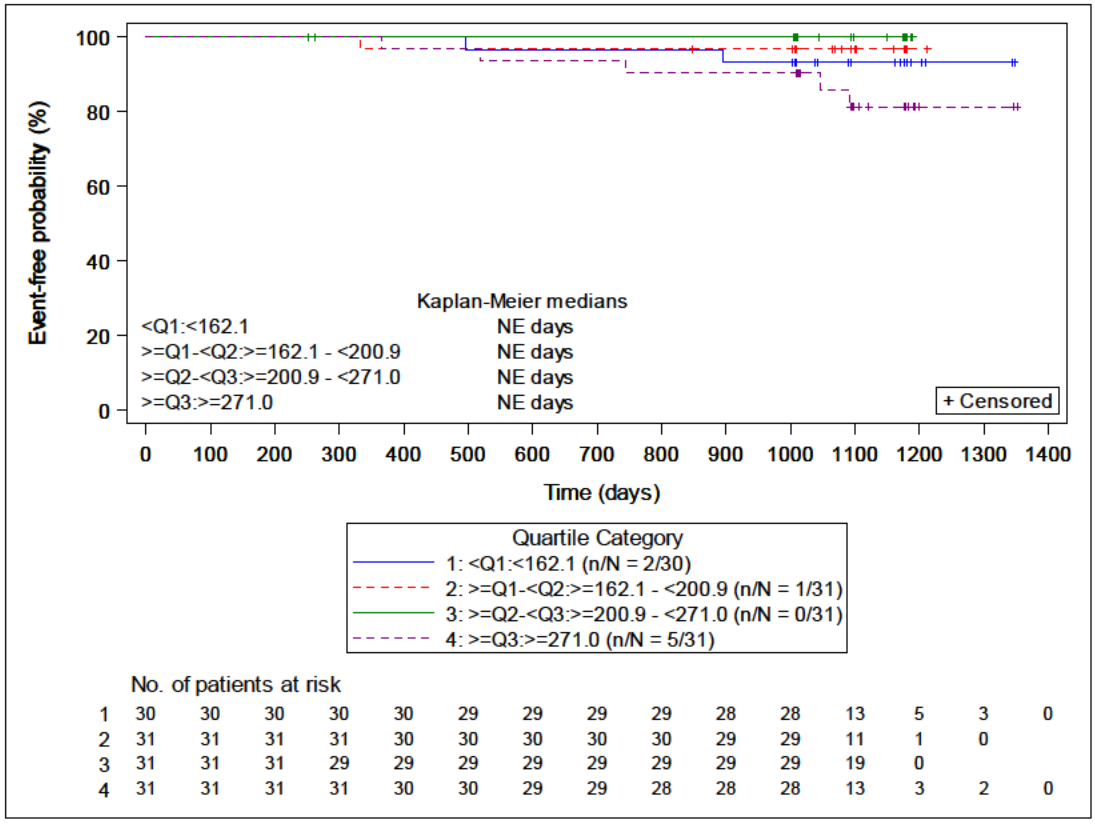
19.4.2.2 ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		To characterize the relationship between ribociclib exposure and iDFS.
Study Included		Phase III Study O12301C
Endpoint		Primary: iDFS by investigator assessment
No. of Patients (total, and with individual PK)		N=123, 108 patients had individual PK (blood samples collected)
Population Characteristics	General	Age median: 55.0 years (range: 30-78 years) Weight median (range): 68.0 kg (range: 44.5-112.1 kg) 1 (0.8%) male, 122 (99.2%) female 99 (80.5%) non-Asian, 24 (19.5%) Asian
	Pediatrics (if any)	Not applicable

Dose Included	Study O12301C: Ribociclib 400 mg orally QD on Days 1 to 21 of a 28 day cycle	
Exposure Metrics Explored (range)	Ctrough concentrations on non-zero dosing days.	
Covariates Evaluated	Not applicable	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Not applicable	**N/A**
Model Parameter Estimates	Not applicable	**N/A**
Model Evaluation	Not applicable	**N/A**
Covariates and Clinical Relevance	Not applicable	**N/A**
Simulation for Specific Population	Not applicable	**N/A**
Visualization of E-R relationships	Figure 6	**Acceptable**
Overall Clinical Relevance for ER	The relationship between Ctrough concentration quartiles and iDFS events was examined for patients included in the PK-iDFS set; however, no conclusions could be drawn due to limited data.	**Acceptable**
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		**N/A**

Figure 6: Kaplan-Meier plot of iDFS by quartiles of geometric mean of popPK-predicted Ctrough (ng/mL) on non-zero dosing days (PK-iDFS set)



Source: SCP Study O12301C-Figure 3-2

19.4.2.3 ER (safety) Executive Summary

The FDA's Assessment:

The E-R analysis for ribociclib and neutropenia is considered exploratory due to the limited data and range of exposure from one dose level. Among the patients with early breast cancer, there were no clear relationship between ribociclib exposure and grade ≥3 neutropenia.

19.4.2.4 ER (safety) Assessment Summary

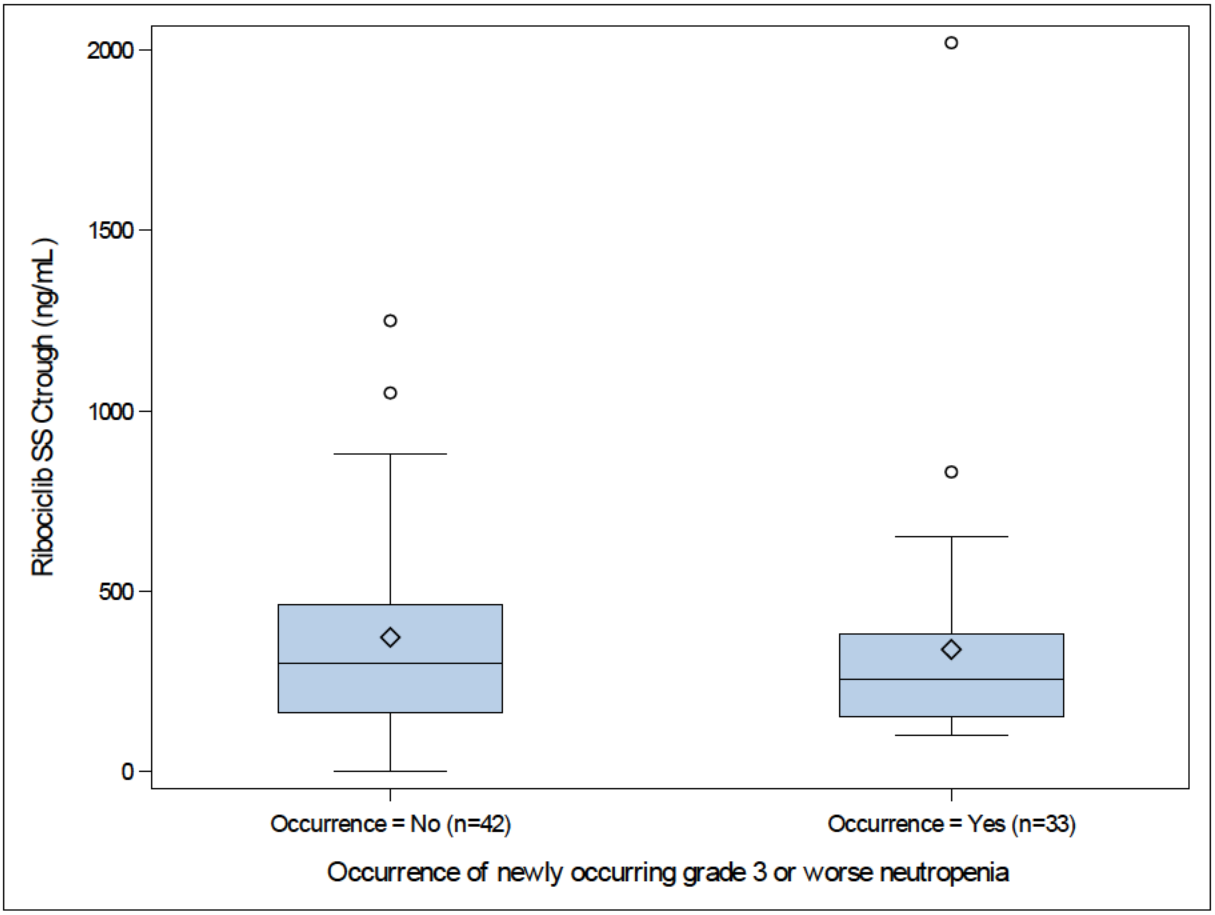
The Applicant's Position:

General Information	
Goal of ER analysis	To characterize the relationship between ribociclib exposure and neutropenia.

Study Included		Study CLEE011O12301C
Population Included		eBC patients from Study O12301C The PK-Neutropenia set includes all patients in the ER-safety set from Study O12301C who had at least one evaluable ribociclib steady-state Ctrough and non-missing baseline neutrophil count. For patients with a newly occurring grade 3 or worse neutropenia post-baseline, at least one evaluable steady-state concentration is required on or before the day of the newly occurring grade 3 or worse neutropenia to be included in the PK-Neutropenia set.
Endpoint		Newly occurring post Baseline grade 3 or worse neutropenia (Yes/No)
No. of Patients (total, and with individual PK)		N=75
Population Characteristics	General	-Age median: 57.0 years (range: 30-78 years) -Weight median: 70.0 kg (range: 45.0-112.1 kg)) -1 (1.3%) male, 74 (98.7%) female - 65 (86.7%) non-Asian, 10 (13.3%) Asian
	Organ impairment	Not applicable
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	22 (29.3%) subjects >=65 yr
Dose(s) Included		Ribociclib 400 mg orally QD on Days 1 to 21 of a 28 day cycle (up to 36 months of treatment)
Exposure Metrics Explored (range)		Evaluable ribociclib SS Ctrough on C1D15

Covariates Evaluated	Not applicable	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Graphical description	**Acceptable**
Model Parameter Estimates	Not applicable	**N/A**
Model Evaluation	Not applicable	**N/A**
Covariates and Clinical Relevance	Not applicable	**N/A**
Simulation for Specific Population	Not applicable	**N/A**
Visualization of E-R relationships	Figure 7	**Acceptable**
Overall Clinical Relevance for ER	In Study O12301C, the Ctrough values of eBC patients with vs. without Grade ≥ 3 neutropenia largely overlap with no apparent difference, which might be due to limited sample size and variability of Ctrough.	**Acceptable**
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		**N/A**

Figure 7: Boxplot of evaluable ribociclib SS Ctrough (ng/mL) collected on C1D15 by occurrence of newly occurring grade 3 or worse neutropenia (PK-Neutropenia set)



Source: SCP Study O12301-Figure 3-3

General Information	
Goal of ER analysis	To further characterize the PK-QTcF relationship between ribociclib concentration and changes from baseline of QTcF to estimate the ΔQTcF values at the ribociclib dose of 400 mg, the starting dose used in Study O12301C, and to further assess the effect of covariates such as patient population on QTcF prolongation.
Study Included	The data of ribociclib + ET arm from Study O12301C was pooled with the data from ribociclib treatment arms in Study A2207 and the studies included in the last update

		report dated 07-May-2018: X1101, X2101, X2107 (Only ribociclib + letrozole patients), A2301, E2301 (only ribociclib + NSAI patients) and F2301.
Population Included		eBC, aBC, and other advanced cancer patients
Endpoint		ΔQTcF (change from baseline of QTcF) with a matched ribociclib concentration was used as a response variable.
No. of Patients (total, and with individual PK)		N=1372 PK-ECG set
Population Characteristics	General	-Age median: 58.0 years (range: 22-96 years) -Weight median: 69.0 kg (range: 34.2-158.8 kg) -75 (5.5%) male, 1297 (94.5%) female -1194 (87.0%) non-Asian, 178 (13.0%) Asian
	Organ impairment	Not applicable
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	436 (31.8%) subjects >=65 yr
Dose(s) Included		• Study O12301C: Ribociclib 400 mg orally QD on Days 1 to 21 of a 28 day cycle • Study A2207, X1101, : Ribociclib 400 mg/600 mg orally QD 3 weeks on/1week off • Studies E2301, F2301, A2301, X2107: Ribociclib 600 mg once daily taken on Days 1-21 of a 28-day cycle • Study X2101: Ribociclib 50/ 70/ 140 / 260/ 280/ 350/ 400/ 600/ 750/ 900/ 1200 mg 3 weeks on / 1 week off for all doses + continuous dosing for 300/400/600 mg
Exposure Metrics Explored (range)		Cmax at C1D15 following a stable 400 mg ribociclib dosing regimen

Covariates Evaluated	In the updated PK-QTcF model, a new covariate, population (eBC vs advanced cancer patients, where advanced cancer patients denote any non-eBC patients, which include aBC patients, in the PK-ECG set), was considered for model selection compared to the previously submitted model [QT/QTc Safety Analysis Report Studies E2301/F2301] and was shown to be statistically significant ($p<0.001$). All the other covariates evaluated in the previous model (M3/7 QT report) were retained and the corresponding parameter estimates are consistent between the updated model and the previous model.	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Linear mixed model	
Model Parameter Estimates	Table 38	
Model Evaluation	Model selection based on goodness of fit using AIC value	
Covariates and Clinical Relevance	The final PK-QTcF model showed that baseline QTcF, combination partner (NSAI vs. fulvestrant vs. no combination) and population (eBC vs. aC) were significantly associated with ΔQTcF among the covariates that were considered, while age (< 40, ≥ 40 to < 65, ≥ 65), sex, and race (Asian vs. non-Asian) were not statistically significant. Patients in eBC population had lower ΔQTcF (-5.37 ms) than advanced cancer population at the same level of ribociclib concentration	
Simulation for Specific Population	Not applicable	

Visualization of E-R relationships	Figure 8	
Overall Clinical Relevance for ER	Using the updated PK-QTcF model of pooled data including Study O12301C, at the popPK model predicted geometric mean steady-state Cmax (1010 ng/mL) of the ribociclib 400 mg dose in the eBC population with NSAI (letrozole or anastrozole) as combination partner, the estimated mean ΔQTcF was 10.0 ms (90% CI: 8.02, 11.91). Patient population is a significant covariate in the PK-QTcF analysis and the eBC population had lower ΔQTcF (-5.37 ms) than the aBC population at the same level of ribociclib concentration.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		

Table 38: Estimated mean QTcF change from baseline from QTcF–ribociclib concentration model (PK-ECG set)

Concentration level	Concentration (ng/mL)	Baseline QTcF (ms)	Estimated mean QTcF change from baseline (ms) (90% CI)
Population = Early breast cancer, Combination partner = NSAI (letrozole or anastrozole)			
400 mg Cmax combo*		419.0	
Geo-mean	1010		10.0 (8.02, 11.91)
Q1	807		8.6 (6.65, 10.49)
Median	999		9.9 (7.93, 11.82)
Q3	1200		11.1 (9.11, 13.07)

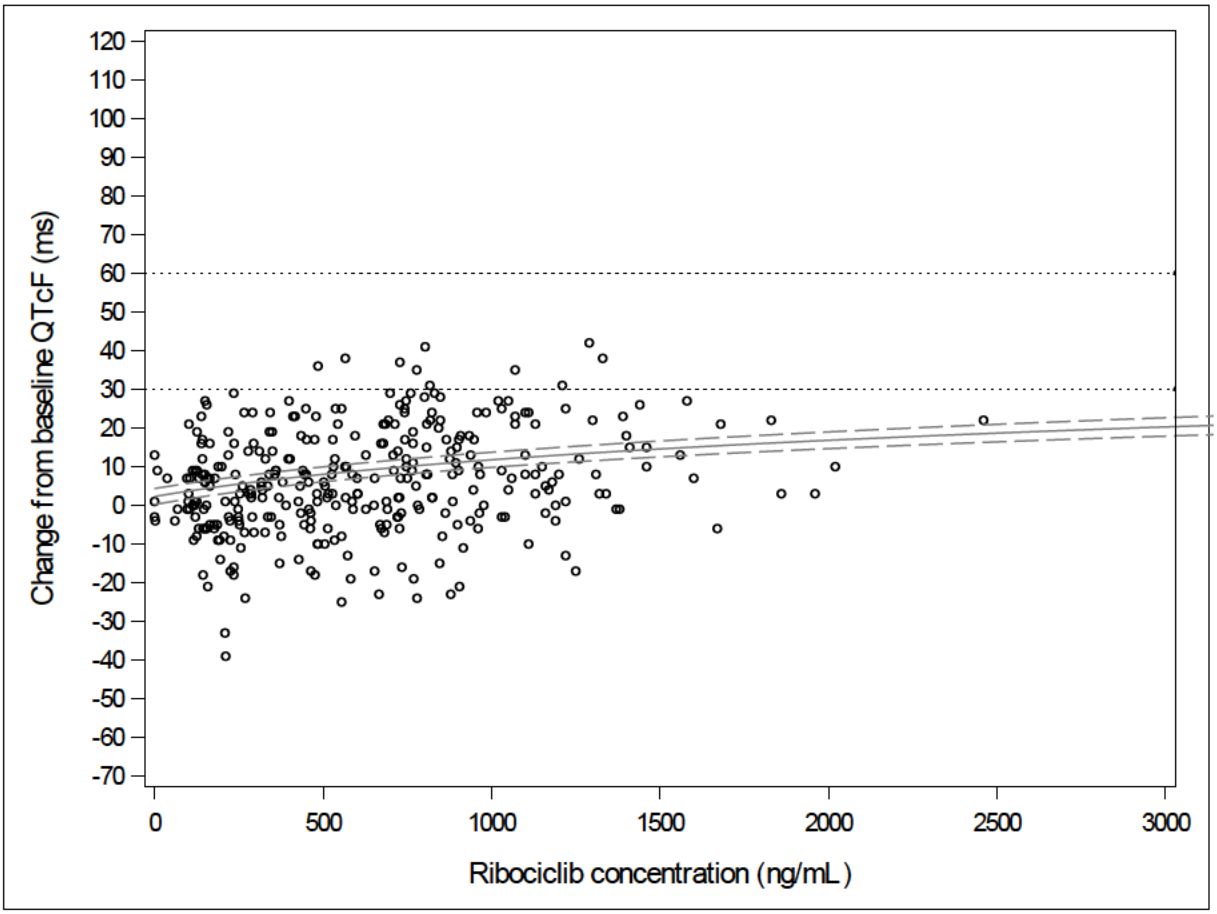
Concentration level	Concentration (ng/mL)	Baseline QTcF (ms)	Estimated mean QTcF change from baseline (ms) (90% CI)

* Based on C1D15 predicted Cmax (from PopPK model) from O12301C using the study level PK Analysis Set.
The model is a linear mixed model with patient as a random effect, and mean function in the form of ΔQTcF = log(concentration/median concentration + 1) + (baseline QTcF – median baseline QTcF) + combination + population + combination* log(concentration/median concentration + 1).

Source: SCP Study O12301C Appendix 1-Table 3-1.5

Figure 8: Scatter plot of QTcF change from baseline versus ribociclib concentration with PK-QT model and 90% CI (PK-ECG set)

Population = eBC, Combination Partner = NSAI (letrozole or anastrozole)



The plot shows a linear mixed model with patient as a random effect, and mean function in the form of Delta QTcF = log(concentration/median concentration + 1) + (baseline QTcF - median

baseline QTcF) + combination + population + combination* log(concentration/median concentration + 1).

Horizontal dotted lines are the reference lines at 30 ms and 60 ms.

Source: SCP Study O12301C Appendix 1-Figure 3-1.2

The FDA's Assessment:

The Applicant's E-R analyses for ribociclib and neutropenia are considered acceptable for the purpose of exploring the relationship between ribociclib exposure and neutropenia in patients with early breast cancer.

19.4.2.5 ER Review Issues

The FDA's Assessment:
No substantive issue.

19.4.2.6 Reviewer's Independent Analysis

The FDA's Assessment:
Reviewer's independent analysis was not performed.

19.4.2.7 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Efficacy in patients with eBC was demonstrated by the statistically significant improvement of both the primary endpoint of iDFS and the secondary endpoints of RFS and DDFS. Due to limited sample size of patients with iDFS events, exposure-efficacy relationship cannot be characterized. The PK-QT modeling confirmed the exposure-QTcF relationship in eBC patients, and patient population is a significant covariate where eBC patients showed less QTcF response than aBC patients. In Study O12301C, the ribociclib Ctrough values of eBC patients with vs. without Grade ≥ 3 neutropenia largely overlap with no apparent difference, which might be due to limited sample size and variability of Ctrough. Both neutropenia and QTcF prolongation, the adverse events related to ribociclib PK exposure, are lower in eBC patients in Study O12301C at the dose of 400 mg than in aBC patients at the dose of 600 mg, supporting improved tolerability of 400 mg dose in eBC patients

Collectively, the exposure response analyses and the safety and efficacy result of NATALEE support the use of ribociclib 400 mg in combination with ET (letrozole or anastrozole) in patients with HR-positive, HER2-negative eBC [CO Study O12301-Section 3.2 and 3.3].

The FDA's Assessment:

Refer to other clinical pharmacology sections of the Assessment Aid for the FDA review.

19.4.3 Physiologically based Pharmacokinetic Modeling Review

The FDA's Assessment:

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's Physiologically based Pharmacokinetic (PBPK) analyses to predict the interaction effects of strong and moderate CYP3A4 modulators on the PK of ribociclib.

The Division of Pharmacometrics has reviewed the PBPK submission (Report DMPK R2300859 and modeling files) to conclude the following:

- **PBPK analyses were adequate to predict the interaction effect of a strong CYP3A inhibitor (ritonavir) and a moderate CYP3A inhibitor (erythromycin) on ribociclib exposure at steady state. The model predicted that coadministration of ritonavir may increase ribociclib AUC_{tau} by 1.8-fold and 1.6-fold, respectively, for 400 mg QD and 600 mg QD doses of ribociclib, respectively. Coadministration of erythromycin may increase ribociclib AUC_{tau} by 1.2-fold and 1.1-fold, respectively, for 400 mg QD and 600 mg QD doses of ribociclib, respectively.**

- **PBPK analyses were adequate to predict the interaction effect of a moderate CYP3A inducer (efavirenz) on ribociclib exposure at steady state. The model predicted that coadministration of efavirenz may decrease ribociclib AUC_{tau} by 74% and 71% for 400 mg QD and 600 mg QD doses of ribociclib, respectively.**

1. Background

Ribociclib (KISQALI) is kinase inhibitor, approved for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy; or fulvestrant. The recommended dose of KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily (QD) for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. KISQALI can be taken with or without food. KISQALI is available as a tablet containing 200 mg ribociclib (KISQALI USPI, 2022).

(b) (4)

The proposed therapeutic dose of KISQALI is 400 mg (two 200 mg film-coated tablets) QD for 21 consecutive days followed by 7 days off.

Ribociclib is primarily metabolized by CYP3A4. Following coadministration of ribociclib (single 400 mg dose) with the strong CYP3A4 inhibitor ritonavir (100 mg twice a day (BID) for 14 days) in healthy subjects, ribociclib C_{max} and AUC increased by 1.7- and 3.2-fold, respectively (Study CLEE011A2101). Following administration of ribociclib (single 600 mg dose) with the strong CYP3A4 inducer rifampin (600 mg QD for 14 days), ribociclib C_{max} and AUC_{inf} decreased by 81% and 89%, respectively, in healthy subjects.

Ribociclib is clinical strong inhibitor of CYP3A4. Following multiple doses of ribociclib (400 mg QD for 8 days) to healthy subjects, midazolam C_{max} and AUC_{inf} increased by 2.1-fold and 3.8-fold, respectively (Study CLEE011A2106). Administration of ribociclib at 600 mg QD is predicted to increase midazolam C_{max} and AUC by 2.4-fold and 5.2-fold, respectively (KISQALI USPI 2022).

Ribociclib exhibited over-proportional increases in exposure C_{max} and AUC across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. The PK nonlinearity was attributed to a decrease of the apparent clearance (CL/F) with increasing dose, possibly due to the autoinhibition of CYP3A4 metabolism. The geometric mean CL/F of ribociclib ranged from 40 to 78 L/h at 600 mg dose across studies in healthy subjects, while the geometric mean CL/F was 25.5 L/h (66% CV) at steady state following 600 mg dose in patients with advanced cancer (Ribociclib Approved USPI, 2017). In patients with early breast cancer following the 400 mg dose, the estimated population mean steady-state CL/F was 38.4 L/h. The CL/F values in patients with early breast cancer seemed approximately 20% higher than that in patients with metastatic breast cancer at both 400 mg and 600 mg dose levels.

The Applicant proposed that these reported difference in the apparent clearance between early or metastatic breast cancer populations may be due to a combined effect of the PK nonlinearity and population differences. Ribociclib is a substrate of CYP3A4, which can be downregulated in patients with cancer, resulting in lower clearance and higher exposure of its substrates (Schwenger et al 2018). Consequently, compared to patients with advanced cancer, the slightly higher clearance and lower exposure of ribociclib at the same dose level of 400 mg in patients with early breast cancer could be due to less disease burden in latter patients. Based on these rationale, two PBPK population models representing healthy volunteers and metastatic breast cancer patients have been described in the literature to characterize the PK of ribociclib in these populations (Samant et al 2020). The main difference of the two population models was a lower CYP3A4 abundance for the cancer patient population model compared to the healthy volunteer model to account for the lower CL/F of ribociclib reported in cancer patients.

In the original submission, PBPK analysis was used predict the DDI effects of strong and moderate CYP3A4 modulators on the PK of ribociclib at steady state in patients with metastatic breast cancer (therapeutic dose of 600 mg QD). In this submission, the Applicant provided new labeling statements for drug interactions (Sections 7 and 12.3) for the proposed therapeutic dose for the early breast cancer population (400 mg QD), (b) (4)

The objective of this PBPK analysis was (1) to evaluate the updated model of ribociclib and proposed cancer population model to describe ribociclib PK in breast cancer patients and

(2) to predict the DDI effects of strong and moderate CYP3A4 modulators on the PK of ribociclib in patients with breast cancer.

2. Methods

Software: **The PBPK analyses were performed using the software Simcyp® Version 22.**

***PBPK population models*: Simulations were performed using modified versions of the healthy volunteer (Sim-Healthy Volunteers) or cancer (Sim-Cancer) population models.**

The Applicant made the following modifications in the healthy volunteer population model: The coefficient of variance (CV) of microsomal protein per gram of liver was reduced to 12% and the CV for the hepatic CYP3A4 abundance was reduced to 23.8% with the intend to match the clinically observed PK variability of ribociclib in healthy subjects and patients with advanced cancer. This modification was firstly implemented in the updated ribociclib model described in Samant et al. 2020. The magnitude of CV reduction for these two parameters had been previously proposed to better predict the clinical variability of the exposure of CYP3A4 substrates (Cubitt et al. 2011). This population model is referred to "adapted healthy volunteer" population in this review.

The Applicant also proposed to develop a population model representing "metastatic breast cancer population", (b) (4)

Ribociclib PBPK model: **A PBPK model for ribociclib was submitted and reviewed by FDA in the original NDA submission (FDA Multi-discipline Review Ribociclib, 2017). This original ribociclib PBPK model, combined with the default healthy volunteer population model (Sim-Healthy Volunteers), was considered sufficient to predict the ribociclib PK and DDI effect as a victim with CYP3A modulators and as a perpetrator with CYP3A substrates, for patients with metastatic breast cancer. The model was then updated for a newer version of the software (V18), as described in the literature (Samant et al., 2020). In this submission, the Applicant further updated the ribociclib model using a newer version of the software (V22) and a first-order absorption model was used to characterize the oral absorption of ribociclib (as in the original model). The performance of the model for PK and DDI effect predictions was evaluated in this review. The input parameters for the PBPK model of ribociclib are summarized in Table 39.**

***PBPK models for the CYP3A modulators*: The software's compound files (V22) for ritonavir (Ritonavir_FO), erythromycin (SV-erythromycin-EC), rifampin (SV-Rifampicin-MD), and efavirenz (SV-Efavirenz) were used without modification.**

Table 39: Input parameters for ribociclib PBPK model

Parameter	Description	Unit	Value	Comment
Physiological and binding property				
MW	Molecular weight	g/mol	434.54	
Log P	Octanol-water partition	-	1.954	
Compound type	-	-	Diprotic base	
pKa1/pKa2	-	-	8.52 / 5.63	Samant et al 2020
B/P ratio	Blood to plasma drug concentration ratio	-	1.01	
fu	Fraction unbound in plasma	-	0.30	
Main plasma binding protein	-	-	Human serum albumin	
Absorption				
Absorption model	First order absorption	-		
fa	Fraction available from dosage form	-	1.00	assumed
CV fa	Coefficient of variation fa	%	30	1)
ka	Absorption rate constant	1/h	0.700	optimized
CV ka	Coefficient of variation ka	%	30	1)
Lag time	-	h	1.10	optimized
CV lag time	Coefficient of variation lag time	%	30	1)
fu(gut)	Unbound fraction in enterocytes	-	1	
Q(gut)	Nominal flow in gut model	L/h	10.9	Samant et al 2020
CV Q(gut)	Coefficient of variation Q(gut)	%	30	
Papp Caco-2	Caco-2 permeability (apical to basal)	10^{-6} cm/s	1.78	
Papp propranolol	Reference compound permeability	10^{-6} cm/s	3.48	
Distribution				
PBPK model	-	-	Full PBPK – Method 2	
Tissue model	-	-	Perfusion limited	
Vss	Volume of distribution at steady-state	L/kg	13.3	Samant et al 2020
CV Vss	Coefficient of variation Vss	%	30	
Kp scalar	Correction factor for Vss	-	3.26	
Enzyme phenotyping (human liver microsomes; HLM)				
Vmax (CYP3A4)	*In vitro* maximum enzyme velocity	pmol/min/mg	318	
Km (CYP3A4)	*In vitro* Michaelis-Menten constant	µM	6.67	Samant et al 2020
fu(inc) (CYP3A4)	Fraction unbound *in vitro*	-	1.0	
Other distribution and elimination property				
In vivo CL	Total clearance	L/h	40.2	Samant et al 2020
CLr	Renal clearance	L/h	1.22	Samant et al 2020
In vitro CL				
Uptake hep	Total hepatic uptake clearance / passive diffusion in hepatocytes	-	1.0	
HLM CLint	Additional undefined HLM CLint	µL/min/mg	16.8	
CV HLM CLint	Coefficient of variation HLM CLint	%	30	
fu(inc) in HLM	Fraction unbound in HLM incubates	-	1.0	Samant et al 2020
CLint(hep)	Overall biliary clearance	µL/min/10^6 cells	0	
CV CLint(hep)	Coefficient of variation CLint(hep)	%	30	

Interaction				
CYP inhibition (competitive)				
Ki (CYP1A2)	Inhibition constant	µM	13.1	Samant et al, 2020
fu(inc) (CYP1A2)		-	1.0	
Ki (CYP3A)		µM	35	
fu(mic) (CYP3A)		-	0.86	
CYP inhibition (time-dependent)				
KI (CYP3A)	Inhibition constant	µM	8.60	Samant et al, 2020
kinact (CYP3A)	Inactivation rate of enzyme	1/h	1.0	
fu(inc) (CYP3A)		-	1.0	

[1] For CV(%) values of input parameters, Simcyp original value (30%; Version 22) was used; otherwise noted.
[2] Hepatic intrinsic clearance due to FMO3-mediated metabolism is represented.

Source: PBPK Report DMPK R2300859, Table 6-1.

Data analysis: **For DDI predictions, the AUC and C_{max} ratios were defined as the geometric mean and 90% confidence interval (CI). Prediction error (PE) was calculated as PE = (predicted value -observed value)/observed value × 100.**

3. Results

3.1 Predictive performance of ribociclib PBPK model for DDI in healthy subjects

Using the updated ribociclib PBPK model and the "adapted healthy volunteer" population model, the predicted DDI effect of ribociclib, as a CYP3A perpetrator and CYP3A victim agreed with the observed data in healthy subjects.

The DDI effect of the strong CYP3A4 inhibitor ritonavir and the strong CYP3A inducer rifampicin on the PK of ribociclib was reasonably described (PE <±35%). Furthermore, the ribociclib model recovered the interaction effect of ribociclib, as a strong inhibitor of CYP3A4, on the PK of the CYP3A substrate midazolam (PE<±12%) (Table 40).

Table 40: Predicted and observed DDI effect of ribociclib as a CYP3A perpetrator or CYP3A victim

Perpetrator dose regimen	Victim dose regimen	Source	Geometric Mean Cmax (%CV) (ng/mL) of victim drug Not inh./inh.	Observed Geometric Mean AUC (%CV) (ng*h/mL) of victim drug Not inh./inh.	Victim drug geometric Mean Cmax ratio (90% CI)	Victim drug geometric Mean AUC ratio (90% CI)
Ribociclib 400 mg QD for 8 days	Midazolam 2 mg SD at day 8	Observed [3]	7.85 (28.4)/16.1 (22.6)	17.7 (26.9)/66.4 (33.3)	2.05 (1.88, 2.23)	3.75 (3.41, 4.11)
		Predicted	7.46 (66.6)/17.0 (59.3)	20.5 (67.3)/85.8 (90.1)	2.28 (2.18, 2.38)	4.18 (3.84, 4.55)
Ritonavir 100 mg BID for 13 days	Ribociclib 400 mg SD day 2	Observed [4]	357/597	5840/18700	1.67 (1.52, 1.84)	3.21 (2.95, 3.49)
		Predicted	469 (36.0)/657 (31.9)	5395 (34.6)/17062 (35.4)	1.40 (1.38, 1.42)	3.16 (3.04, 3.29)
Rifampicin 600 mg QD for 13 days	Ribociclib 600 mg SD day 5	Observed [4]	565/107	8940/953	0.190 (0.164, 0.219)	0.107 (0.0945, 0.120)
		Predicted	671 (35.1)/300 (59.2)	8304 (37.1)/1922 (62.2)	0.447 (0.422, 0.474)	0.231 (0.214, 0.249)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; HV, healthy volunteer; inh, inhibited; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 50% female for the midazolam and ritonavir studies and 20.8% for the rifampicin study. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-2 and Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib and midazolam single dose.

[3] observed HV midazolam Cmax, AUCinf and their ratios at day 8 taken from (CLEE011A2106)

[4] observed HV ribociclib Cmax, AUCinf and their ratios taken from (CLEE011A2101)

Source: Table 6-4 of PBPK Report DMPK R2300859.

3.2 Predictive performance of ribociclib model for PK in healthy subjects and patients with cancer

The PK of ribociclib was predicted following administrations of single intravenous dose of 150 mg and single oral dose of 600 mg to healthy volunteers, and multiple oral dose administration of 400-600 mg QD to late cancer patients and 400 mg QD to early breast cancer patients (Table 41, Figure 9, Figure 10).

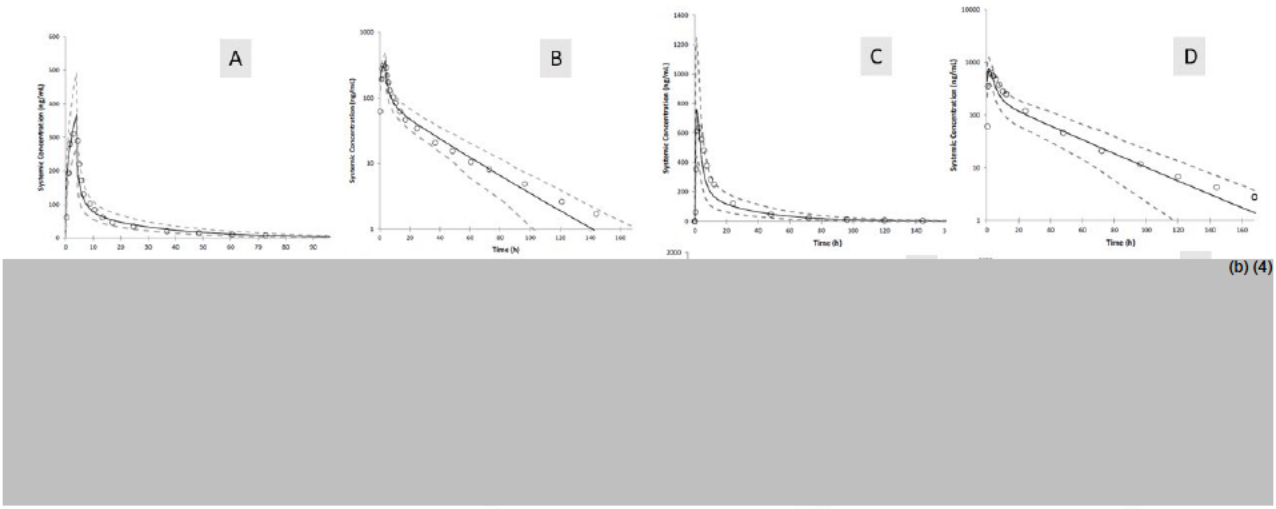
Table 41: PBPK predicted and observed PK parameters or plasma concentrations of ribociclib

Dose regimen	Clinical study population	Observed Cmax (ng/mL)	Predicted* Cmax (ng/mL)	Observed AUC (ng.h/mL)	Predicted* AUC (ng.h/mL)
150 mg SD iv	HV[1]	347 (23)	aHV:363 (19)[$]	3781 (27)	aHV:3781 (21)[$]
600 mg SD	HV[1]	624 (43)	aHV:728 (36)[$]	9840 (44)	aHV:8865 (37)[$]
400 mg QD	late cancer[2,3]	1040 (49)	aHV:923 (36)[$] CP: (b) (4)	11400 (58)	aHV:10828 (49)[$] CP: (b) (4)
600 mg QD[4]	late cancer[2,3]	1820 (62)	aHV:1522 (35)[$] CP: (b) (4)	23800 (66)	aHV:18994 (48)[$] CP: (b) (4)

400 mg QD[4]	Metastatic breast cancer[5]	1080 (58)	aHV:923 (36)[$] CP: (b) (4)		16400 (52)	aHV:10828 (49)[$] CP: (b) (4)	
600 mg QD[4]	Metastatic breast cancer[5]	1500 (67)	aHV:1522 (35)[$] CP: (b) (4)		28600 (50)	aHV:18994 (48)[$] CP: (b) (4)	
Dose regimen	Clinical study population	Observed 2h (ng/mL)	Predicted 2h (ng/mL)	Observed 4h (ng/mL)	Predicted 4h (ng/mL)	Observed 24h (ng/mL)	Predicted 24h (ng/mL)
400 mg QD	Early breast cancer[6]	815 ± 379	aHV:871 ±342 CP (b) (4)	819 ± 366	aHV:869 ±307 CP: (b) (4)	325 ± 272	aHV:306 ±183 CP: (b) (4) (b) (4)

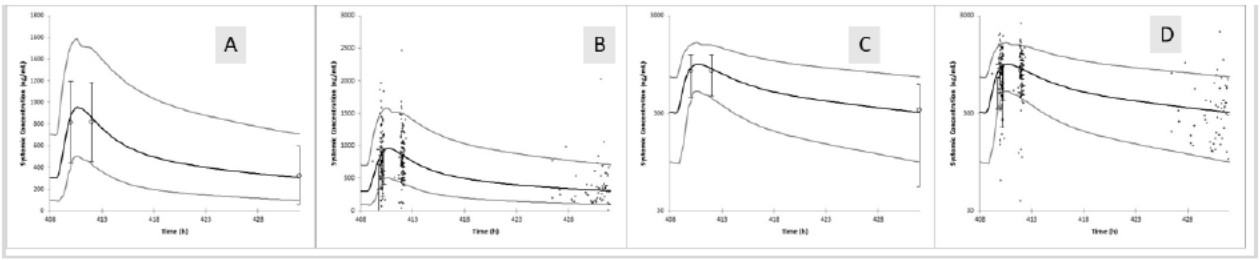
%CV, percent coefficient of variance; aHV, adapted healthy volunteer population model, CP: metastatic breast cancer population model; HV, healthy volunteer; iv, intravenous; QD, once a day; SD, single dose.
PK data are geometric means and %CV. AUC values are AUCinf for single dose and AUCtau at steady-state.
[*]The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. Predictions using either the [$]adapted healthy volunteer (HV) or [&]metastatic breast cancer patient (CP) population model.
[1]Observed ribociclib Cmax and AUCinf at day 1 for 150 and 600 mg SD doses taken from A2117.
[2]Late cancer refers to patients with advanced solid tumor or lymphomas.
[3]Observed ribociclib Cmax and AUCtau at day 18/21 for 400 and 600 mg QD doses taken from X2101.
[4]Reviewer's analysis using Applicant's submitted workspaces files 51 and 52, with dose changed to 600 mg QD.
[5]Observed ribociclib Cmax and AUCtau at day 15 for 400 and 600 mg QD doses taken from A2207.
[6]Observed (n=100-113 per time point) ribociclib plasma concentrations at time points 2-, 4- and 24-hours post-dose of 400 mg QD administration to early breast cancer patients up to 18 days taken from NATALEE trial.
Source: Reviewer adapted from Tables 6-3 and 6-5 of PBPK report DMPK R2300859, simulation output files 7 and 8, reviewer's analysis, Study A2207 CSR and Study A2101 CSR.

Figure 9: Predicted and observed plasma concentration-time profiles of ribociclib in healthy subjects and patients with late cancer



Linear (A) and log-linear (B) PK profile of a single intravenous 4h infusion of 150 mg ribociclib to healthy subjects. Observed mean PK data from Study CLEE011A2117 (circles). Solid black and dashed lines: predicted mean and 5th-95th percentiles for the simulated population (N = 100, 10 x 10 trials), using the "adapted healthy volunteer" population model
Linear (C) and log-linear (D) PK profile of a single oral dose of 600 mg ribociclib to healthy subjects. Observed mean PK data from Study CLEE011A2117 (circles). Solid black and dashed lines: predicted mean and 5th-95th percentiles for the simulated population (N =100, 10 x 10 trials), using the "adapted healthy volunteer" population model
Linear (E) and log-linear (F) PK profile of Day 1 of multiple oral doses of 400 mg QD ribociclib to late cancer patient population. Observed mean PK data from Study CLEE011X2101 (circles). Solid black and gray lines: predicted mean and 5th-95th percentiles for the simulated population (N = 100, 10 x 10 trials), using the "metastatic breast cancer patient" population model.
Linear (G) and log-linear (H) PK profile of Day 18 of 400 mg QD ribociclib to late cancer patient population. Observed mean PK data from Study CLEE011X2101 (circles). Solid black and gray lines: predicted mean and 5th-95th percentiles for the simulated population (N = 100, 10 x 10 trials), using the "metastatic breast cancer patient" population model.
Source: Figures 6-1 and 6-2 of PBPK Report DMPK R2300859

Figure 10: Predicted and observed plasma concentration-time profiles of ribociclib in patients with early breast cancer



Linear (A and B) and log-linear (C and D) PK profile of observed means (A and C) or individual subject concentrations (B and D) of Day 18 of 400 mg QD ribociclib to early breast cancer patients. Observed PK data (circles) and standard deviation (error bars) from NATALEE trial. Solid black and gray lines: predicted mean and 5th-95th percentiles for the simulated population (N = 100, 10 x 10 trials), using the "adapted healthy volunteer" population model.
Source: Simulation Output file 7- PBPK Report DMPK R2300859.

Discussion about the predictive performance of the Applicant's modified population models for ribociclib PK in patients with breast cancer

The performance of the two population models, namely "adapted healthy volunteer" and "metastatic breast cancer patient", were evaluated for their ability to describe the observed PK profile of ribociclib in patients with late cancer and early breast cancer (i.e., patients enrolled in the NATALEE trial receiving ribociclib 400 mg QD).

The steady state PK parameters following administration of ribociclib 400 mg and 600 mg QD to late cancer (Study X2101) and metastatic breast cancer patients (Study A2207) tended to be underpredicted (PE values ≤ -35%) when using the "adapted healthy volunteer" population model (Table 41). Conversely, the plasma concentrations on day 18, following administration of ribociclib 400 mg QD in early breast cancer patients, were fairly predicted with PE values < ±7% by the "adapted healthy volunteer" model (Table 41). Using the "metastatic breast cancer patient" population model, the plasma concentrations in metastatic breast patients tended to be overpredicted (PE values around (b) (4) %) (Table 41), as the result of a somewhat lower CL/F of ribociclib (b) (4) L/h) when using the virtual cancer population model with reduced CYP3A4 abundance (Table 42).

Table 42: Comparison of ribociclib CL/F reported in clinical studies, estimated by Population PK analysis and predicted by PBPK analysis

Population	Dose (mg)	Geometric mean CL/F (%CV)	N	Study
Virtual HV	400 QD	37.0 (49.0)	100	PBPK analysis[1]
Virtual CP	400 QD	(b) (4)	100	PBPK analysis[1]
Virtual HV	600 QD	31.6 (47.7)	100	PBPK analysis[1]
Virtual CP	600 QD	(b) (4)	100	PBPK analysis[1]
HV	400 SD	68.5 (36.4)	24	A2101
HV	400 SD	97.6 (53.2)	14	A2116
HV	400 SD	64.8 (35.2)	11	A2109
HV	400 QD	37.7 (33.5)[2]	25	A2106
HV	600 SD	67.1 (51.4)	24	A2101

HV	600 SD	61.1 (44.4)	16	A2117
HV	600 SD	49.8 (60)	24	A2111(DiC, fasting)
HV	600 SD	42 (32.3)	23	A2111(Tablet, fasting)
HV	600 SD	67.1 (51.4)	24	A2101
HV	600 SD	61.1 (44.4)	16	A2117
Late cancer3	400 QD	35.3 (59.2)	4	X2101
Metastatic breast cancer	400 QD	24.4 (51.8)	17	A2207
Late cancer3	600 QD	25.5 (65.7)	53	X2101
Metastatic breast cancer	600 QD	21.0 (50.0)	13	A2207
Late cancer3	600 QD	26.5 (53.2)	20	X2107
Early breast cancer	400 QD	(b) (4)		Population PK
Early breast cancer	600 QD			Population PK (M3/7 model)
Metastatic breast cancer	600 QD			Population PK (M3/7 model)

%CV, percent coefficient of variance; CP, cancer population; DiC: drug in capsule; HV, healthy volunteer; N, number of subjects; QD, once a day; SD, single dose

[1] The PBPK simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" or "metastatic breast cancer patient (CP)" population model. [2] CL/F value calculated by dose (400 mg) divided by geometric mean $AUC_{0\text{-}24h}$ 400 mg QD (10600 ng.h/mL, A2106-Table 11-13).

[3] "Late cancer" refers to patients with advanced solid tumor or lymphomas.

Source: Reviewer modified from Table 6-2 of PBPK Report DMPK R2300859.

The Reviewer did not consider the proposed "metastatic breast cancer patient" population model sufficiently justified based on the following reasons:

- **Currently, there is no consensus on the clinical effect of cancer on CYP3A abundance. The default cancer population model (Simcyp V22) assumes no alterations on CYP3A abundance in patients with cancer compared to healthy subjects, based on analysis of literature data by the software's developer (data not shown). Additionally, research from Cheeti et al. (2013) suggested that CYP3A activity is not altered in patients with cancer based on PBPK modeling of midazolam exposure. This finding is supported by Baker et al. (2004), which examined CYP3A activity in 134 patients with cancer and found no significant changes related to age, sex, or body size. In contrast, CYP3A downregulation has been reported in patients with cancer during an acute inflammatory response (Coutant et al., 2015). This alteration (30% reduction in hepatic and intestinal CYP3A4 abundance) has been investigated in a PBPK study demonstrating a better prediction of exposure to sensitive CYP3A4 substrates (midazolam and simvastatin) in patients with cancer (Schwenger et al., 2018).**

- **The Applicant's proposed [redacted]. It is not appropriate to change physiological parameters to describe drug-specific effects. Testing these model assumptions with data from other sensitive CYP3A substrates in patients with late cancer and/or metastatic breast cancer would be needed. At current stage, the proposed 'metastatic breast cancer patient' population model is not adequately validated.**

- **Ribociclib showed high inter-subject variability in PK parameters within the same dose and population (i.e., healthy subjects, late cancer patients and early and metastatic breast cancer patients). For example, the coefficient of variation for CL/F range from [redacted]% (Table 42).**

- **Predictions using either population models "adapted HV" or "metastatic breast cancer patient", characterizing the PK of patients with early breast cancer or late cancer had prediction errors lower that the reported variability (%CV) in PK parameters, as demonstrated in this analysis (Table 41) and in the publication used reference for the "metastatic breast cancer patient" model (Samant et al. 2020). According to Samant et al (2020): "Without the adjustment of CYP3A4 expression level, the model predictions would underestimate the exposure in patients with advanced cancer, resulting in down-shifted residual values of ~ 30%".**

- **We acknowledged the perceived difference in ribociclib CL/F among different populations. The difference in CL/F values between the metastatic breast cancer and early breast cancer population seems lower than the reported variability in CL/F. The population PK estimated steady state CL/F was approximately 20% higher in patients with early breast cancer compared to that in patients with metastatic breast cancer at the dose levels of 400 mg QD ([redacted] L/h, respectively) and 600 mg QD ([redacted] L/h, respectively).**

- **A disease-burden effect in late cancer patients affecting PK may be possible. However, attributing this effect to reduction of CYP3A abundance in late cancer patients, but not early cancer, has not being sufficiently proven and is further convoluted by the dose and time-dependent nonlinear PK of ribociclib autoinhibition of CYP3A.**

- **Using a population model with lower CYP3A abundance would result in lesser interaction effect with CYP3A modulators. This approach may only proceed with further confirmatory data and evidence.**

Therefore, the Reviewer concluded that the "adapted healthy volunteer" population model can describe the observed PK in both breast cancer patient populations for the intended purpose. The following DDI simulations were conducted using this population model.

3.3 Model Application: Prediction of the effect of CYP3A modulators on the PK of ribociclib

PBPK simulations were conducted to predict the DDI effect of moderate (erythromycin) and strong CYP3A inhibitors (ritonavir) and moderate (efavirenz) and strong CYP3A inducers (rifampicin) on the PK of ribociclib in early and metastatic breast cancer patients (Table 43 and Table 44).

A slightly dose and time-dependent (i.e., single dose vs steady state) interaction effect on the PK of ribociclib was predicted with CYP3A inhibitors due to autoinhibition effect of ribociclib on CYP3A4.

Following administration of the strong CYP3A4 inhibitor ritonavir (100 mg BID, for 14 days) with a single dose of 400 mg ribociclib, the model predicted similar increase in ribociclib exposure (predicted AUCinf and C_{max} ratios of 3.1- and 1.4-fold, respectively) as observed in the clinical DDI study in healthy subjects (observed AUC_{inf} and C_{max} ratios of 3.2 and 1.7, respectively). Administering ribociclib 400 mg QD for 8 days in the presence of ritonavir, a lower DDI effect was predicted with AUC_{tau} and C_{max} ratios of 1.84 and 1.47, respectively. The predicted C_{max} and AUC_{tau} of ribociclib in presence of ritonavir was 1322 ng/mL and 19401 ng.h/mL. Following administration of ribociclib 200 mg QD in the presence of ritonavir, a slightly higher DDI effect compared to ribociclib 400 mg QD was predicted due to less autoinhibition of CYP3A4. The predicted AUC_{tau} and C_{max} ratios are 2.51 and 1.76, respectively. Consequently, the predicted ribociclib exposure at 200 mg QD in the presence of ritonavir (AUC_{tau}=9695 ng.h/mL) was comparable to the predicted exposure at 400 mg QD without inhibitor (AUC_{tau}=10523 ng.h/mL) (Table 43**). Also, the predicted exposure of ribociclib at 400 mg QD dose in presence of ritonavir (AUC_{tau} and C_{max} of 19401 ng.h/mL and 1322 ng/mL, respectively) is lower than its reported exposure at the 600 mg QD dose (standard dose for metastatic breast cancer therapy) in patients with late cancer (AUC_{tau} and C_{max} of 23800 ng.h/mL and 1820 ng/mL, Study X2101). Therefore, for patients with early breast cancer, a dose reduction from 400 mg QD to 200 mg QD in the presence of a strong CYP3A inhibitor is justified. Administering ribociclib 600 mg QD for 8 days in the presence of ritonavir, the predicted AUC_{tau} and C_{max} ratios were 1.56 and 1.33, respectively (Table 43). The predicted ribociclib exposure at 400 mg QD in the presence of ritonavir (AUC_{tau}=19401 ng.h/mL) was comparable to the predicted exposure at 600 mg QD without inhibitor (AUC_{tau}=18696 ng.h/mL). Therefore, for patients with metastatic breast cancer, a dose reduction from 600 mg QD to 400 mg QD in the presence of a strong CYP3A inhibitor is justified and in agreement with conclusions from the original submission (FDA Multidiscipline Review Ribociclib, 2017).**

No clinically meaningful interaction was predicted with the coadministration of the moderate CYP3A4 inhibitor erythromycin (500 mg BID, for 8 days) with ribociclib 400 mg QD (predicted AUC_{tau} and C_{max} ratios of 1.23 and 1.13, respectively) and ribociclib 600 mg QD (predicted AUC_{tau} and C_{max} ratios of 1.13 and 1.08, respectively) (Table 43).

Table 43: PBPK predicted AUC and C_{max} of ribociclib in the absence and presence of CYP3A4 inhibitors

Perpetrator	Source	Ribociclib dose regimen [1]	Inhibition status	Geometric Mean Cmax (%CV) (ng/mL)	Geometric Mean AUC (%CV) (ng*h/mL)	Geometric Mean Cmax ratio (90%CI)	Geometric Mean AUC ratio (90% CI)
Ritonavir 100 mg BID for 14 days	simulated	600 mg SD on day 8	- inhibitor + inhibitor	807 (29.3) 1163 (25.2)	9646 (35.9) 30250 (38.2)	1.44 (1.42, 1.46)	3.14 (3.00, 3.28)
Ritonavir 100 mg BID for 8 days	simulated	600 mg QD for 8 days	- inhibitor + inhibitor	1496 (35.2) 1984 (28.9)	18696 (46.5) 29114 (35.5)	1.33 (1.29, 1.36)	1.56 (1.50, 1.62)
Ritonavir 100 mg BID for 14 days	observed	400 mg SD on day 2	- inhibitor + inhibitor	357 597	5840 18500	1.67 (1.52, 1.84)	3.21 (2.95, 3.49)
Ritonavir 100 mg BID for 14 days	simulated	400 mg SD on day 2	- inhibitor + inhibitor	518 (28.6) 769 (24.6)	5749 (33.5) 18966 (33.6)	1.40(1.38, 1.40)	3.14 (3.03, 3.27)
Ritonavir 100 mg BID for 8 days	simulated	400 mg QD for 8 days	- inhibitor + inhibitor	900 (35.5) 1322 (28.9)	10523 (47.1) 19401 (35.5)	1.47 (1.43, 1.51)	1.84 (1.76, 1.93)
Ritonavir 100 mg BID for 14 days	simulated	200 mg SD on day 2	- inhibitor + inhibitor	249 (28.7) 388 (25.3)	2641 (32.6) 10079 (38.2)	1.56 (1.53, 1.58)	3.82 (3.64, 4.00)
Ritonavir 100 mg BID for 8 days	simulated	200 mg QD for 8 days	- inhibitor + inhibitor	375 (33.5) 661 (28.9)	3855 (42.5) 9696 (35.5)	1.76 (1.72, 1.82)	2.51 (2.40, 2.63)
Erythromycin 500 mg BID for 8 days	simulated	600 mg SD on day 8	- inhibitor + inhibitor	807 (29.3) 987 (28.9)	9659 (36.0) 16272 (42.8)	1.22 (1.21, 1.24)	1.68 (1.63, 1.74)
Erythromycin 500 mg BID for 8 days	simulated	600 mg QD for 8 days	- inhibitor + inhibitor	1496 (35.2) 1617 (33.3)	18696 (46.5) 21168 (43.0)	1.08 (1.07, 1.09)	1.13 (1.12, 1.14)
Erythromycin 500 mg BID for 8 days	simulated	400 mg SD on day 8	- inhibitor + inhibitor	521 (29.1) 648 (29.0)	5862 (34.3) 10285 (42.6)	1.24 (1.23, 1.26)	1.75 (1.69, 1.82)
Erythromycin 500 mg BID for 8 days	simulated	400 mg QD for 8 days	- inhibitor + inhibitor	900 (35.5) 1021 (33.7)	10523 (47.1) 12912 (44.0)	1.13 (1.12, 1.14)	1.23 (1.21, 1.24)
Erythromycin 500 mg BID for 8 days	simulated	200 mg SD on day 8	- inhibitor + inhibitor	249 (28.7) 317 (29.0)	2642 (32.7) 4787 (42.1)	1.27 (1.26, 1.29)	1.81 (1.74, 1.88)
Erythromycin 500 mg BID for 8 days	simulated	200 mg QD for 8 days	- inhibitor + inhibitor	375 (33.5) 468 (33.5)	3855 (42.5) 5593 (43.9)	1.25 (1.23, 1.26)	1.45 (1.42, 1.48)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

[3] observed ribociclib Cmax and AUCtau at day 18/21 for a 600 mg QD dose: 1820 ng/mL and 23800 ng*h/mL (CLEE011X2101)

Source: Table 6-6 of PBPK Report.

Following administration of the strong CYP3A4 inducer rifampin (600 mg QD, for 13 days) with a single 600 mg dose of ribociclib, the model predicted a comparable decrease in ribociclib AUC_{inf} (77%) as observed in the clinical DDI study in healthy subjects (decrease in AUC_{inf} by 89%). A similar decrease in ribociclib AUC_{tau} (around 83-80%) was predicted following administration of ribociclib 400 mg QD or 600 mg QD at steady state (Table 44). Therefore, concomitant use of ribociclib with strong CYP3A4 inducers should be avoided.

Following administration of the moderate CYP3A4 inducer efavirenz (600 mg BID, for 14 days) with ribociclib 400 mg QD or 600 mg QD dose, a moderate interaction effect was predicted. The predicted decreases in AUC_{tau} and C_{max} of ribociclib were 74% and 55%, respectively, for 400 mg QD and 71% and 52%, respectively, for 600 mg QD. These

decrease in ribociclib exposure in the presence of efavirenz was comparable to the predictions for a single 400 mg or 600 mg dose of ribociclib (AUC_{inf} decreased by 69%.

Table 44: PBPK predicted AUC and C_{max} of ribociclib in the absence and presence of CYP3A4 inducers

Perpetrator	Source	Ribociclib dose regimen [1]	Induction status	Geometric Mean C_{max} (%CV) (ng/mL)	Geometric Mean AUC (%CV) (ng*h/mL)	Geometric Mean C_{max} ratio (90%CI)	Geometric Mean AUC ratio (90% CI)
Rifampicin 600 mg QD for 13 days	observed	600 mg SD on day 5	- inducer + inducer	565 107	8940 953	0.190 (0.164, 0.219)	0.107 (0.0945, 0.120)
Rifampicin 600 mg QD for 13 days	simulated	600 mg SD on day 5	- inducer + inducer	671 (35.1) 300 (59.2)	8318 (37.2) 1922 (62.2)	0.447 (0.422, 0.474)	0.231 (0.214, 0.249)
Rifampicin 600 mg QD for 14 days	simulated	600 mg QD for 14 days	- inducer + inducer	1500 (34.7) 567 (64.7)	18607 (46.2) 3646 (93.3)	0.378 (0.351, 0.407)	0.196 (0.176, 0.218)
Rifampicin 600 mg QD for 14 days	simulated	400 mg SD on day 12	- inducer + inducer	518 (28.6) 206 (53.6)	5753 (33.5) 1149 (59.2)	0.398 (0.374, 0.423)	0.200 (0.185, 0.216)
Rifampicin 600 mg QD for 14 days	simulated	400 mg QD for 14 days	- inducer + inducer	911 (35.6) 311 (60.1)	10633 (48.2) 1813 (77.8)	0.342 (0.318, 0.367)	0.171 (0.155, 0.188)
Rifampicin 600 mg QD for 14 days	simulated	200 mg SD on day 12	- inducer + inducer	248 (28.2) 96.1 (54.2)	2596 (31.9) 520 (59.4)	0.388 (0.364, 0.413)	0.200 (0.185, 0.217)
Rifampicin 600 mg QD for 14 days	simulated	200 mg QD for 14 days	- inducer + inducer	383 (34.4) 124 (56.4)	3986 (45.6) 660 (65.4)	0.324 (0.302, 0.347	0.166 (0.151, 0.181)
Efavirenz 600 mg QD for 14 days	simulated	600 mg SD at day 12	- inducer + inducer	807 (29.3) 450 (36.5)	9659 (36.0) 2967 (44.3)	0.557 (0.537, 0.578)	0.307 (0.288, 0.328)
Efavirenz 600 mg QD for 14 days	simulated	600 mg QD for 14 days	- inducer + inducer	1549 (36.8) 747 (51.0)	19692 (49.4) 5735 (78.7)	0.483 (0.453, 0.514)	0.291 (0.262, 0.324)
Efavirenz 600 mg QD for 14 days	simulated	400 mg SD at day 12	- inducer + inducer	521 (29.1) 286 (36.2)	5866 (34.4) 1842 (43.1)	0.550 (0.530, 0.571)	0.314 (0.295, 0.335)
Efavirenz 600 mg QD for 14 days	simulated	400 mg QD for 14 days	- inducer + inducer	936 (37.2) 421 (47.3)	11189 (50.4) 2907 (67.9)	0.449 (0.424, 0.477)	0.260 (0.236, 0.286)
Efavirenz 600 mg QD for 14 days	simulated	200 mg SD at day 12	- inducer + inducer	249 (28.7) 135 (35.7)	2642 (32.7) 846 (42.1)	0.542 (0.521, 0.563)	0.320 (0.301, 0.341)
Efavirenz 600 mg QD for 14 days	simulated	200 mg QD for 14 days	- inducer + inducer	390 (35.2) 171 (41.2)	4127 (46.3) 1062 (52.6)	0.440 (0.418, 0.463)	0.257 (0.237, 0.279)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

[3] observed ribociclib Cmax and AUCinf at day 1 for a 600 mg SD dose taken from (CLEE011A2117)

Source: Table 6-7 of PBPK Report.

4. Conclusions

A previously developed ribociclib PBPK model was updated in a newer version of the modeling software (Simcyp version V22) and used to support the revised labeling regarding DDI effects (USPI section 12.3). The Applicant proposed updating the DDI results with moderate CYP3A modulators using the updated PBPK model of ribociclib and their modified versions of the healthy volunteer ('adapted healthy volunteer') and cancer ('metastatic breast cancer patient') population models. The reviewer identified limitations in the 'metastatic breast cancer patient' population model and concluded that it was

inadequate to be used to support the proposed labeling edits. Consequently, predictions using the updated ribociclib model and the 'adapted healthy volunteer' population model were used in the USPI section 12.3.

PBPK analyses were adequate to predict the interaction effect of a strong CYP3A inhibitor (ritonavir) and a moderate CYP3A inhibitor (erythromycin) on ribociclib exposure at steady state. The model predicted that coadministration of ritonavir may increase ribociclib AUC_{tau} by 1.8-fold and 1.6-fold, respectively, for 400 mg QD and 600 mg QD doses of ribociclib, respectively. Coadministration of erythromycin is not expected to meaningfully change ribociclib exposure.

PBPK analyses were adequate to predict the interaction effect of a moderate CYP3A inducer (efavirenz) on ribociclib exposure at steady state. The model predicted that coadministration of efavirenz may decrease ribociclib AUC_{tau} by around 70% for 400 mg QD and 600 mg QD doses.

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19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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