NOVARTIS

Patient Safety & Pharmacovigilance

Ribociclib

LEE011

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Ribociclib
Product(s) concerned (brand name(s)):	KISQALI®
Document status:	Final
Version number:	8.2
Data lock point for this RMP	NATALEE: 21-Jul-2023 MONALEESA 2: 10-Jun-2021 PSUR: 12-Mar-2023
Date of final sign off	09-Oct-2024

Template version 6.4, Effective from 12-Dec-2021

Rationale for submitting an updated RMP:

Compared to the European Union (EU) Risk Management Plan (RMP) version 8.1, this version update of the RMP (v 8.2) is being prepared to provide the updates in the indication wording for early breast cancer and inclusion of NATALEE (CLEE011O12301C) post-authorization efficacy study (PAES) in Section 11.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v8.0
Part I	Update in the indication wording for early breast cancer
Part II	No change
Part III	No change
Part IV	Inclusion of NATALEE (CLEE011O12301C) post-authorization efficacy study
Part V	No change-
Part VI	No change
Part VII	Updated Annex 5 and Annex 8

Other RMP versions under evaluation

CCI

Details of the currently approved RMP:

Version number: 7.0

Approved with procedure: EMEA/H/C/004213/IB/0039
Date of approval (opinion date): 05-Jan-2023

QPPV name: Dr. Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

aBC	Advanced Breast Cancer
ADR	Adverse Drug Reaction
AE	Adverse Events
AIs	Aromatase Inhibitors
ALP	Alkaline Phosphatase
AUC	Area Under The Curve
BCRP	Breast Cancer Resistance Protein
BSEP	Bile Salt Export Pump
CDK	Cyclin-Dependent Kinases
Cmax	Maximum Plasma Concentration
CTC	Common Terminology Criteria
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DCO	Data cut off
DILI	Drug Induced Liver Injury
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRS	Electronic Case Retrieval Strategy
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen Receptor
ET	Endocrine Therapy
EU	European Union
FDA	Food and Drug Administration
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor / Hazard Ratio
iDFS	Invasive disease-free survival
MA	Marketing Authorization
MAA	Marketing Authorization Application
MATE	Multidrug and Toxin Extrusion Protein
MedDRA	Medical Dictionary For Regulatory Activities
NCCN	National Comprehensive Cancer Network
NSAI	Non-Steroidal Aromatase Inhibitors
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OS	Overall survival
PAES	Post-authorization efficacy study
PFS	Progression Free Survival

PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PTY	Patient Treatment Years
PVCs	Premature Ventricular Contraction
QTc	QT corrected
QTcB	QTc corrected by Bazett's Formula
QTcF	QT corrected by Fridericia's Formula
RD	Risk Difference
RMP	Risk Management Plan
ROW	Rest Of the World
SAE	Serious Adverse event
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SEER	Surveillance, Epidemiology, And End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
US	United States

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Ribociclib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, protein kinase inhibitors (L01EF02)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	Kisqali 200 mg film-coated tablets
Invented name(s) in the European Economic Area (EEA)	KISQALI®
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Ribociclib is an orally bioavailable, highly selective small molecule inhibitor of cyclin-dependent kinases (CDK) 4/6 that induces cell cycle G1 to S Phase arrest at sub-micromolar concentrations in a variety of cancer cells in vitro.
	Summary of mode of action: Ribociclib inhibits the CDK4/CCND1 and CDK6/CCND3 enzyme complexes with concentrations resulting in 50% inhibition (IC50) values of 0.01 and 0.039 µM in biochemical assays, respectively. CDK4/6 in conjunction with their protein regulator, cyclin D1 (encoded by *CCND1*), a direct transcriptional target of estrogen-receptor signaling, regulate cell-cycle progression. CDK4/6 overexpression and CCND1 amplification are frequently encountered in Estrogen receptor (ER)-positive breast cancers and are key mediators of endocrine resistance.
	Important information about its composition: Active drug substance: ribociclib (as succinate salt) Each film-coated tablet contains approximately 7.83 mg polyvinyl alcohol and 0.34 mg lecithin (soy) (E322) List of excipients: • Tablet core: Microcrystalline cellulose, Crospovidone type A, Low substituted hydroxypropylcellulose, Magnesium stearate, Colloidal anhydrous silica Film coating: Colloidal silicon dioxide, crospovidone (Type A), low-substituted hydroxypropylcellulose, iron oxide black (E172), iron oxide red (E172), soya lecithin (E322), magnesium stearate, microcrystalline cellulose, polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide (E171), xanthan gum
Hyperlink to the Product Information	[Proposed SmPC] [Current approved SmPC]:

Indication(s) in the EEA	**Current:** Kisqali is indicated for the treatment of patients with HR+/HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. In pre- or perimenopausal women, endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
	Proposed: Kisqali is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence. In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.
Dosage in the EEA	**Current:** Advanced or Metastatic Breast Cancer: Ribociclib 600 mg (three 200 mg film-coated tablets), once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. Ribociclib should be used together with 2.5 mg letrozole or another aromatase inhibitor. The aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the prescribing information for letrozole or another aromatase inhibitor for additional details. Kisqali can be taken with or without food. Patients should be encouraged to take their dose at approximately the same time each day.
	Proposed: Early breast cancer: The recommended dose is 400 mg (two 200 mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. In patients with early breast cancer, Kisqali should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur. When Kisqali is used in combination with aromatase inhibitor (AI), the AI should be taken orally once daily continuously throughout the 28 day cycle. In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a LHRH agonist.
Pharmaceutical form(s) and strengths	Current (if applicable): Film-coated tablets 200 mg.
	Proposed (if applicable): There are no changes to the pharmaceutical form and strength
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indications and target population

2.1 Indication: HR-positive, HER2-negative early breast cancer

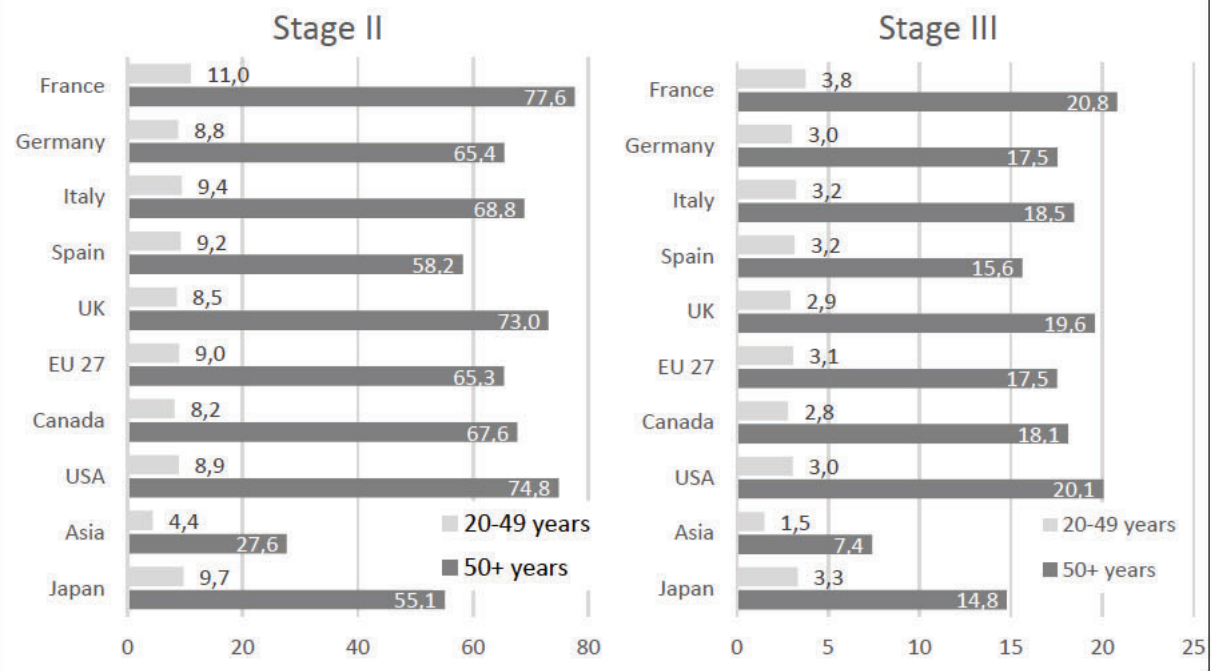
Breast cancer is the most frequently diagnosed cancer worldwide. Approximately 2.3 million new cases of BC and 685,000 deaths attributed to this disease were estimated to occur in 2020 worldwide. Across Europe, the estimated incidence of all types of breast cancer in 2020 was approximately 531,000, with 142,000 deaths (GLOBOCAN 2020). Almost all newly diagnosed breast cancer cases are early breast cancer, localized to the breast tissue and regional lymphatics, which are potentially curable with locoregional treatment modalities such as surgery and radiation therapy.

Among early breast cancer disease, Stage II and Stage III resectable tumors are at risk of recurrence (Stage III unresectable tumors are considered advanced breast cancer). However, there are no robust epidemiological estimates of the proportion of all Stage III breast cancers that are resectable. Therefore, estimates presented below of early breast cancer at risk of recurrence include all of Stage II and III breast cancer. The numbers presented as part of Stage III incidence and prevalence are therefore an overestimate of early Stage III breast cancers.

Incidence

In the European Union of 27 member states (EU27) in 2020, the estimated incidence rates of Stage II and Stage III HR-positive HER2-negative breast cancer among women per 100,000 population-year were 9.0 and 3.1, respectively, in pre-menopausal women and 65.3 and 17.5, respectively, in post-menopausal women. The incidence rates were relatively similar between European countries and North America and lower in Asia (Figure 2-1).

Figure 2-1 **Estimated incidence rate (per 100,000 population) of HR-positive HER2-negative early breast cancer by cancer stage and age group**



Incidence rates are normalized to the world population

Menopausal status was defined using a cut-off of 50 years old as a proxy: <50 pre-menopausal and ≥50 post-menopausal

*Incidence rate of breast cancer was based on:

1) Breast cancer incidence (Globocan 2020) in women aged <50 and 50+

2) SEER (US cancer registry) 5-year incidence based on 2011, 2012, 2013, 2014, 2015, proportion HR-positive HER2-negative breast cancer in women aged <50 (Stage II:25.91%, Stage III: 8.88%) and 50+ (Stage II: 23.8%, Stage III: 6.38%) (SEER)

Calculation: (1) x (2)

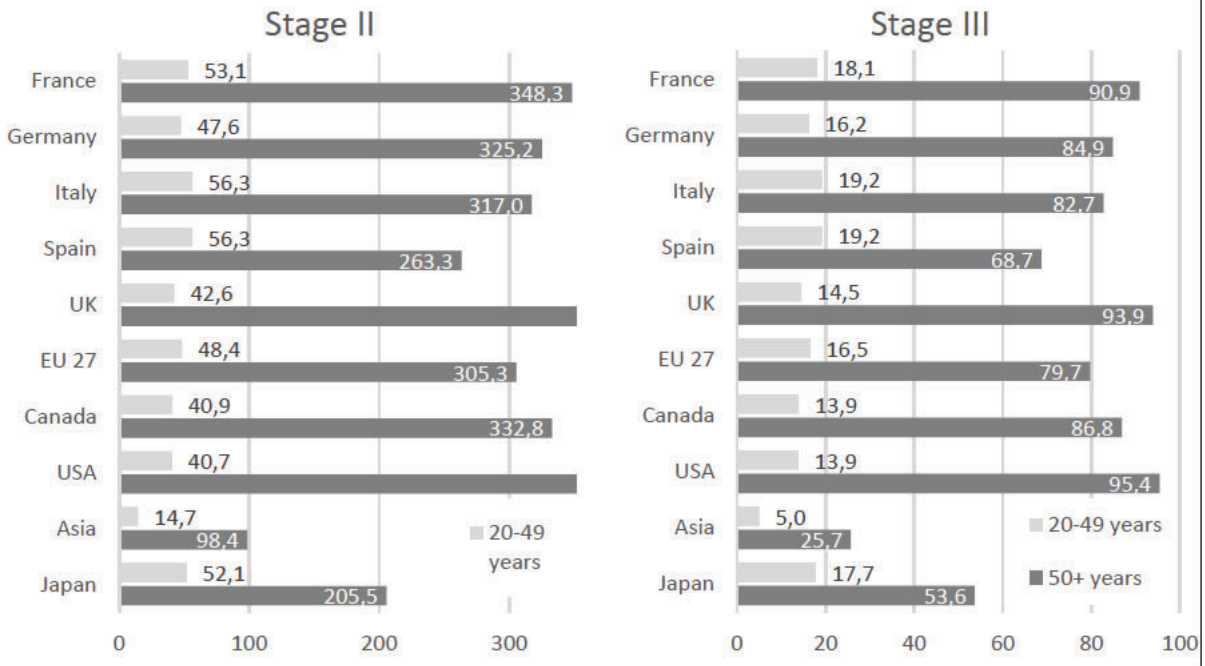
Data sources in 2020 reported a range of incidence rates of breast cancer (all stages, all subtypes) between 137.2 (crude) and 142.8 (European age-standardized rate) per 100,000 population (Globocan 2020, ECIS 2020), with variation between European countries. Incidence rates were higher in Benelux (Belgium, the Netherlands, and Luxumburg) countries, high in Western and Northern Europe, while lower in Eastern and South Europe, compared to the European Union (EU) average (ECIS 2020).

At the same time, literature sources indicated the proportion of patients diagnosed at Stage II or intermediate/regionalized breast cancer ranged between 23.9% and 41% across European countries (Hübner et al 2020, OECD 2020, Ilic et al 2022), while the proportion of patients with Stage III disease was reported from 10.2% to 17.8% (Baeyens-Fernández et al 2018, Larsen et al 2018) in all breast cancer patients.

Prevalence

In 2020, the 5-year prevalence per 100,000 of Stage II and Stage III HR-positive HER2-negative breast cancer in the EU27 was 48.4 and 16.5, respectively, in pre-menopausal women and 305.3 and 79.7, respectively, in post-menopausal women. As with incidence, the lowest prevalence was observed in Asia (Figure 2-2).

Figure 2-2 Estimated prevalence (per 100,000 population) of HR-positive HER2-negative early breast cancer by cancer stage and age group



Menopausal status was defined using a cut-off of 50 years old as a proxy: <50 pre-menopausal and ≥50 post-menopausal

*5-year prevalence of breast cancer was based on:

1) Breast cancer 5-year prevalence (Globocan 2020) in women aged <50 and 50+

2) SEER (US cancer registry) 5-year limited duration prevalence as of January 2015, proportion HR-positive HER2-negative breast cancer in women aged <50 (Stage II: 27.01%, Stage III: 9.20%) and 50+ (Stage II: 24.89%, Stage III: 6.49%) (SEER 2022)

Calculation: (1) x (2)

The 5-year prevalence of all stages breast cancer in the EU was 640.6 per 100,000 (Globocan 2020). Literature sources estimated the proportion of all breast cancers that were stage II between 21.4% and 36.5%, and between 6.9% and 26.0% for Stage III (Hernandez et al 2014, Spreafico et al 2020) (Table 2-1).

Table 2-1 The prevalence and distribution of breast cancer stages

Location (reference)	Prevalence of breast cancer per 100,000	Proportion in early stages
EU27 (Globocan 2020)	5y, all stages 640.6	Not reported

Germany (Robert Koch Institute 2022)	5y, all stages 364.1* 10y, all stages 669.0* 25y, all stages 1157.7*	Not reported
The Netherlands (Vondeling et al 2018)	5y, all stages 713.0*	Not reported
US, OSCER (Hernandez et al 2014)	1y, all stages NR	Stage I 22.6%* Stage II 21.4%* Stage III 6.9%*
Brazil (Spreafico et al 2020)	15y, all stages NR	Stage 0 7.6% Stage I 21.2% Stage II 36.5% Stage III 26.0%
* Derived from data reported in the article		

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The age distribution of incident cases is similar in Stage II and Stage III. Around a third of newly diagnosed patients are aged between 50 and 69 years, while about half of patients are 70 years old or above in both stages. In Stage III there is a slightly higher proportion of women aged 70 years and older (Katalinic et al 2020, Baeyens-Fernández et al 2018, Spreafico et al 2020). Due to the all-cause and breast cancer specific mortality, the age distribution of prevalent patients shows a lower proportion of patients in the oldest age group (Spreafico et al 2020).

Male breast cancer represents about 1% of all breast cancers diagnosed in the US (Siegel et al 2015). Based on data from the International Agency for Research on Cancer, the highest female-to-male breast cancer incidence rate ratio is observed in Singapore (205 female-to-male ratio) and the lowest in the Philippines (55 female-to-male ratio) (Ly et al 2013).

In the US, population-based studies reported substantial racial and ethnic variation in breast cancer tumor characteristics, based on SEER data. For example, Black, and Hispanic women more likely to be diagnosed with regional (31%) breast cancers, compared with White, Asian/Pacific Islander; or American Indian/Alaska Native women (range 24% to 29%) (Giaquinto et al 2022). Japanese and Non-Hispanic White patients are less likely to be diagnosed with Stage II (32.4% and 33.2%, respectively) or Stage III (8.5% and 11.4%, respectively) breast cancer compared with Hispanic White, Black, South Asian, Other Asian, or Other Ethnicity (Iqbal et al 2015).

Main treatment options

Besides primary surgery, management of patients with HR-positive, HER2-negative eBC typically consists of additional anti-neoplastic treatment modalities including radiation therapy and adjuvant or neoadjuvant systemic chemotherapy and / or endocrine therapy. Although many patients with HR-positive, HER2-negative eBC may be rendered disease-free after initial therapy, distant recurrence due to micro-metastatic disease is common. Distant recurrence is the primary cause of death in patients with eBC (Anampa et al 2015), highlighting an unmet need for therapeutic options that will improve long-term outcomes in this patient population.

While adjuvant ET for HR-positive eBC is effective in reducing the risk of recurrence and improving survival, recurrences and subsequent deaths are still common. This is especially relevant in patients with tumor characteristics indicative of a higher risk of recurrence, including those with Anatomic Stage Groups II and III, among other pathological and genomic features. In a meta-analysis including 60,000 women with ER-positive eBC who were disease-free after 5 years of scheduled ET, cumulative 20-year risk of distant recurrence was 22% in women with no positive nodes (N0), 31% in those with 1-3 positive nodes (N1-3), and 52% in those with 4-9 positive nodes (N4-9), with a strong correlation between annual risk of recurrence and nodal status ($P < 0.001$). The corresponding cumulative 20-year risks of death from BC were similar (15%, 28%, and 49%, respectively). Recurrences, mostly in the form of distant metastases, are generally incurable and will eventually lead to death due to breast cancer (Pan et al 2017). While the risk of recurrence is highest within 2 to 3 years after diagnosis, it persists for at least 20 years, highlighting the need for additional treatment options. As a result, new therapeutic strategies are required to improve clinical outcomes in patients with HR-positive, HER2-negative eBC, at an increased risk of recurrence.

NATALEE (CLEE011O12301C) was conducted to evaluate the efficacy and safety of adjuvant ribociclib combined with standard of care aromatase inhibitor in patients with eBC. The patient population in the study primarily consists of patients with Anatomic Stage II (40.1%) or Stage III (59.6%) disease per AJCC staging (CLEE011O12301C CSR-Section 10.3.1).

The inhibition of CDK4/6 can delay or overcome endocrine resistance and thereby enhance the effectiveness of ET. Several studies suggest that ribociclib treatment of cancer cells induces both G1 phase cell cycle arrest and phenotypes of cellular senescence (Rader et al 2013, Iyengar et al 2018, Kim et al 2018, Mayayo-Peralta et al 2021, Rao et al 2021). In addition, several lines of evidence suggest that ribociclib may promote anti-cancer immune cell responses (Goel et al 2017, Juric et al 2021, Peuker et al 2022). These unique properties of ribociclib may prevent early and late recurrences through direct elimination of replicating tumor cells or by locking dormant cells in a senescent state for immune-mediated clearance, respectively. Based on these results from preclinical and clinical studies, it is hypothesized that ribociclib may induce senescence in micro metastatic tumor cells and an antitumor immune response to ultimately eliminate them.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

In Europe, over the last decades, the 10-year overall survival rates after initial breast cancer diagnosis increased from 87% to 93% for early and 41% to 62% for locally advanced disease (Vondeling et al 2018). In patients with Stage III breast cancer, the median survival ranged between 28 and 66 months across previous studies, and the five-year overall survival (OS) was reported to be between 20% and 56% (Jatoi 2010). Based on SEER data, patients with HR-positive/HER2-negative tumors had 3-year OS of 93.6% for Stage II and 85.5% OS for Stage III (Leone et al 2019).

While many patients with HR-positive, HER2-negative early BC may initially be rendered disease-free, distant recurrence due to micro-metastatic disease is common. After initial therapy, distant recurrence is the primary cause of death in patients with early BC (Anampa et al 2015).

While the risk of recurrence is highest within 2 to 3 years after diagnosis, it persists for at least 20 years, highlighting the need for additional treatment options (Pan et al 2017).

In early-stage breast cancer, acute and chronic side effects stem from chemotherapy, surgery, and radiotherapy. Acute side effects include nausea, vomiting, asthenia, mucositis, and gastrointestinal disorders, while chronic side effects encompass neuropathic pain, scapular periarthritis, and lymphedema (Saghatchian et al 2014). Sleep problems and fatigue are also common side effects of cancer treatment, with prevalence estimates ranging from 20% to 99% (Bower 2008). Postmenopausal women with early-stage breast cancer receiving AIs or tamoxifen treatment experience increased risks of fractures, cardiovascular events, thromboembolic events, and endometrial cancer (Reinhorn et al 2020). Arthralgia, fatigue, alopecia, and depressive feelings or mood alterations are associated with early treatment discontinuation (Blok et al 2018).

Important comorbidities:

In a review on comorbidities in early breast cancer (Land et al 2012), the following comorbidities were most frequently reported:

- hypertension
- cardiovascular disease
- diabetes mellitus
- previous cancer
- chronic obstructive pulmonary disease

2.2 Indication: HR-positive, HER2-negative advanced breast cancer

Epidemiology of the disease

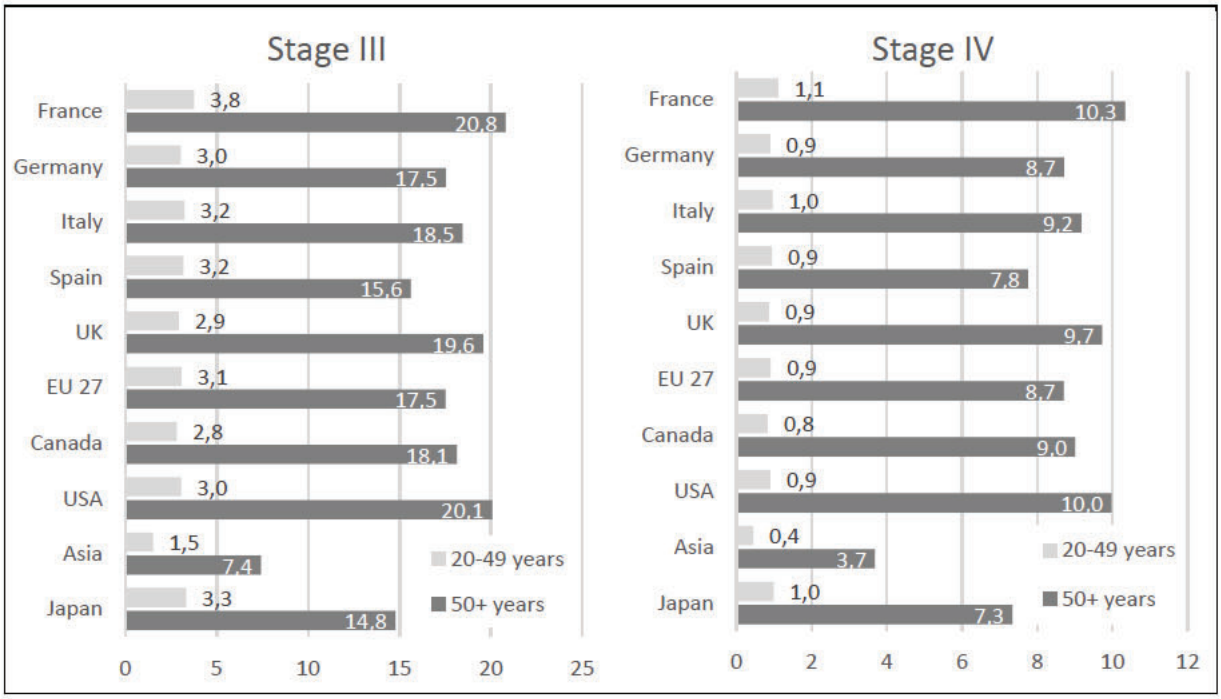
Advanced breast cancer is defined as Stage III unresectable and Stage IV tumors. However, as there are no robust epidemiological estimates of the proportion of all stage III breast cancers that are unresectable, estimates presented below include all of Stage III and Stage IV breast cancer. The numbers presented as part of Stage III incidence and prevalence are therefore an overestimate of the Stage III breast cancers that are advanced.

Incidence

In the EU27_in 2020, the estimated incidence rates of Stage III and Stage IV hormone receptor-positive (HR-positive) human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer among women per 100,000 population-year were 3.1 and 0.9, respectively in pre-menopausal women and17.5 and 8.7, respectively in post-menopausal women. The incidence rates were relatively similar between European countries and North America and lower in Asia (Figure 2-3).

The 5-year prevalence per 100,000 of HR-positive HER2-negative BC in the EU27+UK was 13.9 in pre-menopausal women and 39.6 post-menopausal and, as with incidence, the lowest was observed in Asia (Figure 2-3).

Figure 2-3 Estimated incidence rates (per 100,000 population) of HR-positive HER2-negative advanced breast cancer by cancer stage and age group



Incidence rates are normalized to the world population

Menopausal status was defined using a cut-off of 50 years old as a proxy: <50 pre-menopausal and ≥50 post-menopausal

*Incidence rate of breast cancer was based on:

1) Breast cancer incidence (Globocan 2020) in women aged <50 and 50+

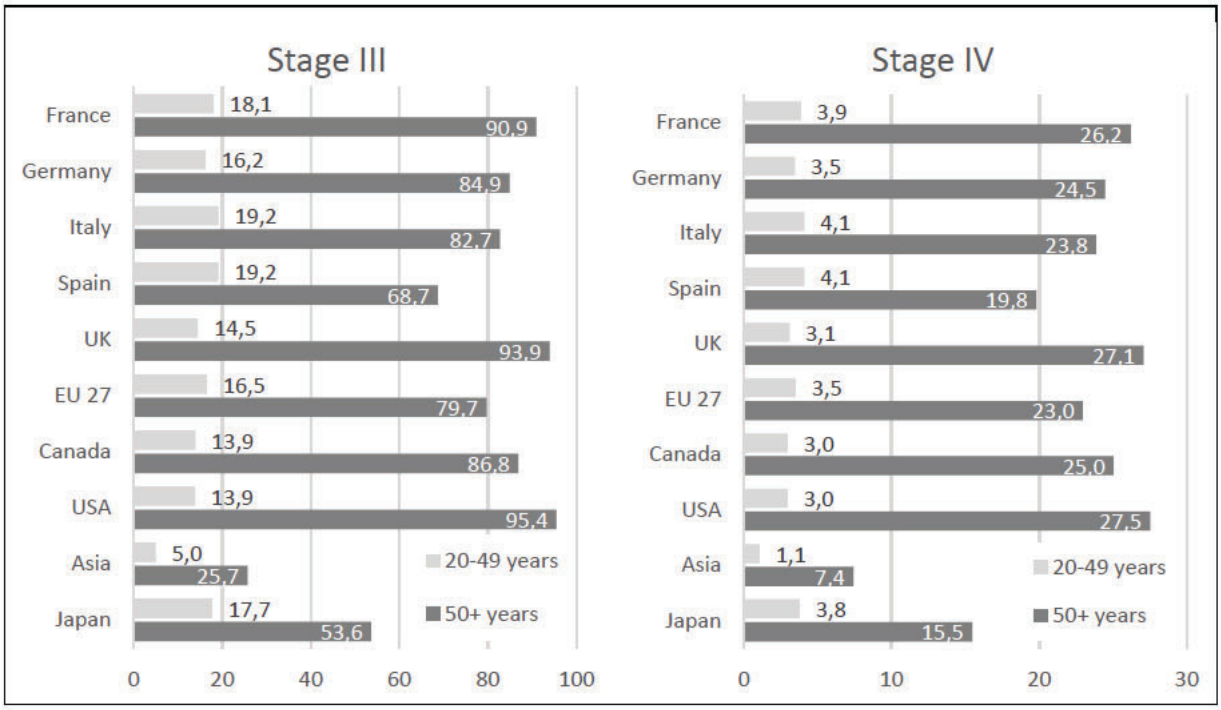
2) SEER (US cancer registry) 5-year incidence based on 2011, 2012, 2013, 2014, 2015, proportion HR-positive HER2-negative breast cancer in women aged <50 (Stage III: 8.88%, Stage IV: 2.64%) and 50+ (Stage III: 6.38%, Stage IV: 3.17%) (SEER)

Calculation: (1) x (2)

Prevalence

In 2020, the 5-year prevalence per 100,000 of Stage III and Stage IV HR-positive HER2-negative breast cancer in the EU27 was 16.5 and 3.5, respectively, in pre-menopausal women and 79.7 and 23.0, respectively, in post-menopausal women. As with incidence, the lowest prevalence was observed in Asia (Figure 2-4).

Figure 2-4 Estimated prevalence (per 100,000 population) of HR-positive HER2-negative advanced breast cancer by cancer stage and age group



Menopausal status was defined using a cut-off of 50 years old as a proxy: <50 pre-menopausal and ≥50 post-menopausal

*5-year prevalence of breast cancer was based on:

1) Breast cancer 5-year prevalence (Globocan 2020) in women aged <50 and 50+

2) SEER (US cancer registry) 5-year limited duration prevalence as of January 2015, proportion HR-positive HER2-negative breast cancer in women aged <50 (Stage III: 9.20%, Stage IV: 1.96%) and 50+ (Stage III: 6.49%, Stage IV: 1.87%) (SEER)

Calculation: (1) x (2)

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

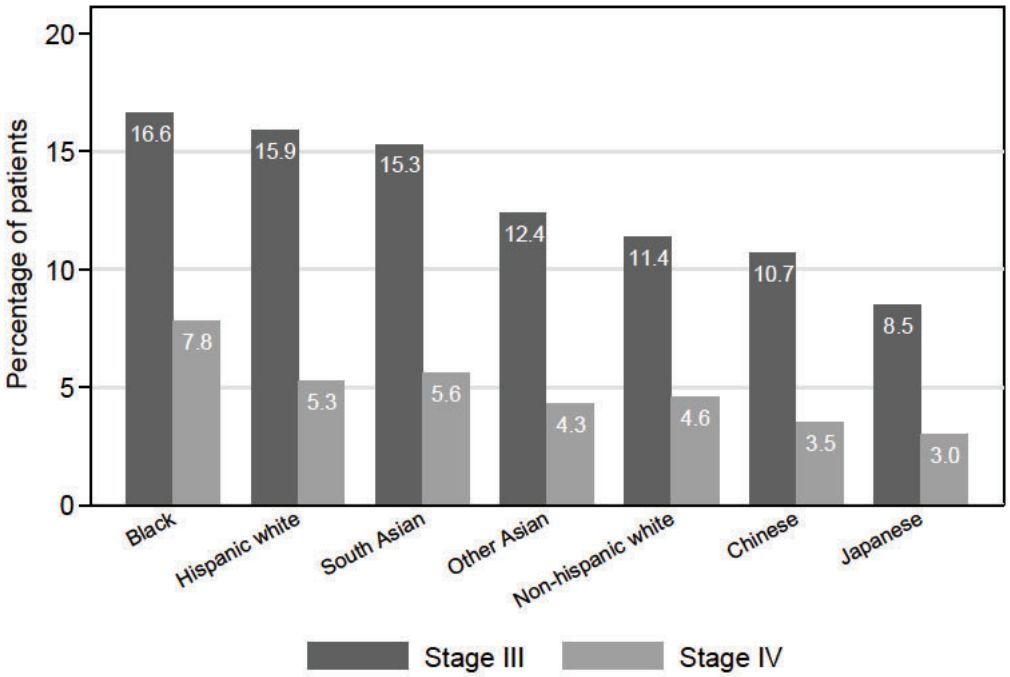
The stage at diagnosis of breast cancer varies with age. Locally advanced and metastatic diseases are more frequently diagnosed in women at older ages (Figure 2-4).

Male breast cancer represents about 1% of all breast cancers diagnosed in the United States of America (US) (Siegel et al 2015). Based on data from the International Agency for Research on Cancer, the highest female-to-male breast cancer incidence rate ratio is observed in Singapore (205) and the lowest in the Philippines (55) (Ly et al 2013).

Incidence rates vary by race/ethnicity group and are generally higher in white women (Acheampong et al 2020). However, Iqbal et al 2015 observed, based on Surveillance, Epidemiology, and End Results (SEER) data, that when stage of the disease at diagnosis by race/ethnicity is analyzed, black women have the highest percentage of Stage IV diagnoses (7.8%) and Japanese population the lowest (3.0%)(Figure 2-5).

The risk of disease progression varies according to the characteristics of the tumor (higher risk in greater tumor size and nodal positivity, and lower in HR-positive), as well as age at diagnosis (Kennecke et al 2010, Lord et al 2012, Colzani et al 2014, Purushotham et al 2014).

Figure 2-5 Stage of breast cancer at diagnosis according to race/ethnicity in the US



Source: Iqbal et al 2015

The main existing treatment options:

The efficacy and overall tolerability of CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) in combination with endocrine therapy have changed treatment options for patients with HR-positive advanced breast cancer. Marked progression-free survival (PFS) benefits in the first-line setting in postmenopausal as well as premenopausal and perimenopausal women receiving aromatase inhibitors (AIs) and any of the three CDK4/6 inhibitors approved, including patients with visceral disease and high risk features. Ribociclib and abemaciclib have also shown statistically significant overall survival benefit in the advanced breast cancer setting (Burstein et al 2021, Gennari et al 2021, NCCN 2021).

Ribociclib is effective in *de novo* or recurrent advanced breast cancer, in cases of primary or secondary endocrine resistance, in postmenopausal or premenopausal women [the latter with a

luteinising hormone-releasing hormone (LH-RH) agonist] and in men (with an LH-RH agonist). Endocrine therapy alone in the first-line setting should be reserved for the small group of patients with comorbidities or a performance status that prevents the use of CDK4/6 inhibitor combinations; there are no clinical or biomarker data that can help to identify patients suitable for endocrine therapy alone. In patients who required first-line chemotherapy due to imminent organ failure, or who did not have access to a CDK4/6 inhibitor in the first-line setting, it is clinically acceptable to use endocrine therapy plus a CDK4/6 inhibitor as a subsequent therapy in cases of progressive disease (Gennari et al 2021).

After progression on a first line CDK4/6 inhibitor plus endocrine therapy, multiple parameters like previous anticancer therapy, disease burden, or mutations will guide the selection of next treatment lines. Multiple combinations of everolimus with exemestane or tamoxifen or fulvestrant are available options. Alpelisib in combination with endocrine therapy should be offered to postmenopausal patients in combination with fulvestrant, and to male patients, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer following prior endocrine therapy including an AI, with or without a CDK4/6 inhibitor. Chemotherapy or poly (ADP-ribose) polymerase (PARP) inhibitors can be proposed for tumours harboring *gBRCAm* (Burstein et al 2021, Gennari et al 2021, NCCN 2021).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Advanced breast cancer is a treatable but still incurable disease (Cardoso et al 2014). Women with advanced breast cancer have a significantly lower survival compared with all patients with breast cancer. The five-year relative survival in patients with breast cancer of all stages, estimates range from 85% or higher in the developed countries to 60% or lower in many less developed countries (Youlden et al 2012) (Table 2-2).

Several factors contribute to the prognosis of women with advanced breast cancer such as hormonal status receptor (lowest breast cancer-specific mortality in women with both estrogen- and progestogen-receptor positive) (Dunnwald et al 2007), site of metastasis (lowest median survival in liver, multiple sites and brain involvement) or patient's age (poor prognosis in ≥50 years) (Largillier et al 2008).

Table 2-2 Relative survival of women with advanced breast cancer

Reference	Country	Relative survival according to stage of the disease	
Allemani et al (2013b)[1]	**10-year survival**	**Regional[2]**	**Metastatic[2]**
	The Netherlands	63%	5%
	Finland	63%	14%
	Norway	65%	9%
	Poland	53%	5%
	Slovenia	55%	5%
	Switzerland	75%	19%
Walters et al (2013)[3]	**3-year survival**	**Stage III**	**Stage IV**
	Canada	83.1%	39.9%
	Denmark	82.7%	35.6%
	Norway	79.2%	31.6%
	Sweden	76.2%	41.8%
	UK	70.2%	27.4%
Foukakis et al (2011)[4]	**3-, 5-year survival**	**-**	**Metastatic**
	Sweden		26.0%/15.2%
USA (SEER Registries)	**USA**	**Stage III**	**Stage IV**
SEER Output 3[5]	3-, 5-, 10-year survival (all BC subtypes)	79.7% / 69.1% / 52.6%	37.1% / 22.8% / 10.0%
SEER Stat Output 4[6]	3-, 4-year survival (Aged 50+ and HR-positive HER2-negative)	87.5% / 82.0%	44.7% / 33.5%
SEER Stat Output 5[6]	3-, 4-year survival (Aged <50 and HR-positive HER2-negative)	90.3% / 85.7%	58.5% / 42.8%

Relative survival is defined as the ratio of the survival observed among the cancer patients and the survival that would have been expected if they had experienced the same death rates as the general population from which they derive. Is a measure usually used in population-based cancer survival studies

[1]Survival was estimated for women who were alive at some point during 2000-2002. For The Netherlands, Poland and Switzerland information refers only to Amsterdam, Warsow and Geneve, respectively. Age-standardized with the International Cancer Survival Standard 1 population

[2]Stage was grouped into the categories specified in the EUROCARE-4 protocol: regional extension (spread to regional lymph nodes) and metastatic (tumor spread to distant organs).

[3]Period 2000-2007. Canada and Sweden covered only specific regions in the country. Age-standardized to stage-specific weights derived from the age distribution of patients in all jurisdictions combined, in the age categories 15–44, 45–54, 55–64, 65–74, 75–84 and 85–99 years

[4]Period 2000-2004

[5]Period 2000-2014. Age-standardized to the International Cancer Survival Standard 1 population

[6]Period 2010-2014. Age-standardized to the International Cancer Survival Standard 1 population

Sources: Allemani et al (2013), Walters et al (2013), Foukakis et al (2011), SEER Output 3, SEER Stat Output 4, SEER Stat Output 5

Adverse events anticipated in the target population

In the advanced breast cancer setting, fatigue, depression, insomnia, and pain are the most common symptoms in addition to those that occur based on the site of metastasis (Irvin et al 2011). Fatigue is the most commonly reported symptom in cancer patients, with an

estimated prevalence of 25%-99% during treatment and 20%-35% off treatment, and insomnia between 20%-70% (Bower 2008). The prevalence of chronic pain in patients with advanced cancer is estimated at 70%–90% (Irvin et al 2011). In Denmark, among 61,709 women with a breast cancer diagnosis, the 100 patient-years incidence rate of affective disorder was 0.13 (95% confidence interval (CI): 0.11, 0.14) and of anxiety disorder 0.05 (95% CI: 0.04, 0.05) (Hjerl et al 2002).

Endocrine therapy is associated with hot flushes and mood disturbances. Tamoxifen increases the risk of pulmonary embolism and endometrial cancer and AIs may cause arthralgia, myalgia and bone loss leading to fractures (Perez 2007, Davies et al 2013, Goss et al 2016). Patients exposed to everolimus may have increased risk of metabolic disorders with hyperglycemia, noninfectious pneumonitis and hematologic disorders (Vicier et al 2014). In patients exposed to chemotherapy or radiotherapy, drug induced interstitial lung disease can be observed and anthracycline-based therapies are associated with cardiotoxicity (clinical decompensation, structural change, biomarker rise or arrhythmia) (Camus et al 2004, Schwaiblmair et al 2012, McGowan et al 2017).

Important co-morbidities:

The prevalence and incidence of the main comorbidities in post-menopausal women is presented in Table 2-3. In women of all ages with breast cancer the prevalence of main comorbidities is (Abdel-Qadir et al 2016) (N=98999):

- Hypertension: 43.0%
- Diabetes: 13.3%
- Prior cancer: 5.0%
- Chronic obstructive pulmonary disease: 4.8%
- Congestive heart failure: 4.5%
- Chronic renal failure: 2.2%
- Acute myocardial infarction: 1.7%
- Cerebrovascular disease: 1.4%
- Peripheral vascular disease: 1.3%

Table 2-3 Prevalence and incidence of comorbid conditions in women diagnosed of Stage III-IV breast cancer (>=65 years old)

	Prevalence (percent of included population) (N=2558)		Three-month after diagnosis incidence rate (per 1000 patient-years) (N=2191)	
Comorbidity	**Stage III**	**Stage IV**	**Stage III**	**Stage IV**
Cardiac/vascular				
Hypertension	51	42.46	611.48	642.25
Coronary artery disease (except myocardial infarction)	18.97	14.01	112.61	152.88

Congestive heart failure	10.16	7.08	122.48	292.86
Cerebrovascular disease	12.53	11.31	94.29	109.35
Atrial fibrillation	8.07	7.9	130	172.74
Arrhythmia	6.76	5.14	114.22	89.43
Myocardial infarction	4.78	3.11	77.43	70.92
Peripheral vascular disease	3.26	2.48	32.99	45.68
Thromboembolism	2.27	2.45	42.52	208.33
Arterial thrombosis	0.29	0.35	4.72	13.3
Cardiac arrest	0.2	0.13	5.49	16.28
Gastrointestinal/hepatic				
Cholecystitis	1.16	1.49	15.2	39.99
Gastric ulcers	0.55	0.65	11.9	24.54
Liver disease	0.33	0.79	7.91	13.86
Metabolic				
Diabetes	16.89	15.39	74.94	132.74
Hyperglycemia	0.05	0	0	3.64
Musculoskeletal/rheumatic				
Osteoarthritis	13.37	9.2	93.23	120.5
Rheumatologic disease	2.09	1.57	8.69	15.75
Neurological/psychiatric				
Alzheimer's disease and dementia	6.05	3.49	79.77	84.64
Depression	4.97	4.92	70.41	171.86
Hemiplegia	1.53	0.95	20.13	22.04
Pulmonary				
Chronic obstructive pulmonary disease	10.41	9.52	133.86	289.19
Renal				
Renal disease	1.52	1.35	19.57	40.32
Nephrotic syndrome	0.06	0.22	0	0
Source: Danese et al 2012.				

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity	
Bone marrow and lymphoid system In rat and dog toxicity studies, bone marrow hypocellularity, reduced extramedullary hemopoiesis in the spleen, lymphoid depletion in the thymus, spleen, gut-associated lymphoid tissues and lymph nodes with reduced germinal center development in the latter occurred. Correlating bone marrow smears and hematological changes also occurred with decreases in myeloid: erythroid ratio, reticulocyte count, red blood cell count, hemoglobin and hematocrit as well as decreases in lymphocytes, neutrophils, monocytes and eosinophils. These changes were reversed or showed a trend towards reversibility and are suggestive of a direct effect of the compound on hematopoiesis and lymphopoiesis and may be related to the pharmacological action of ribociclib.	Neutropenia was the most common toxicity observed in patients. Monitoring of Complete Blood Cell Count (CBC) before and during treatment with ribociclib and as clinically indicated at any time during treatment is recommended. Dose modification and management based on absolute neutrophil count (ANC) is recommended. With dose modification neutropenia is reversible (SmPC).
Hepatobiliary system toxicity The hepatobiliary system was a target organ of toxicity in all rat toxicity studies and in the 4-week dog toxicity study. In rats, the changes were characterized by bile duct epithelium vacuolation and/or hypertrophy. Correlating increase in total bilirubin was also present. In dogs treated up to 4 weeks, the changes consisted of hyperplasia/hypertrophy/proliferation of intrahepatic and extrahepatic bile ducts with periductular fibrosis, inflammatory cells and single cell degeneration; gallbladder hyperplasia/hypertrophy with wall and arterial necrosis and cholestasis; inspissated bile with calculi in gallbladder and arteriopathy with focal wall degeneration. Clinical biochemistry changes indicative of liver toxicity included increases in alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin, as well as an increase in cholesterol, and decrease in triglycerides, glucose and/or albumin and globulin. Proliferative changes within the intrahepatic and extrahepatic biliary tree are often indicative of irritation as a consequence of excretion of the test item and/or its metabolic products via the biliary system as has been established with the metabolic products of ribociclib. Evidence of cholestasis, sand-like gallbladder calculi, and inspissated bile in the gallbladder supported this assumption. The formation of	Hepatobiliary toxicity has been observed in ribociclib clinical trials. Bilirubin increases either in isolation or together with the transaminases elevation have been observed, including few cases meeting Hy's Law criteria. Liver function tests (including transaminases and bilirubin) should be monitored before and during treatment, and as clinically indicated. Dose adjustments or discontinuation should be considered for transaminase increases with or without bilirubin elevations, as described in the prescribing information (SmPC).

large foam cells in the walls of the extrahepatic and common bile ducts and occasionally around major intrahepatic bile ducts may represent local accumulation of the compound or its metabolite(s), nevertheless phospholipidosis cannot be completely ruled out. No relevant alterations of the liver parenchyma were evident. All changes were reversible.	
Gastrointestinal (GI) system In the 2-week dogs toxicity study only, mucosal atrophy mainly in the jejunum was observed. These changes were reversible. In a 1-week tolerability study in females rats, histopathological findings in the non-glandular stomach (ulceration of the epithelium and submucosal infiltration of neutrophils) as well as degeneration and necrosis of the villi of the small intestine were indicative of poor local tolerance at ≥ 600 mg/kg/day (approximately 4 fold the patient area under the curve (AUC) at the recommended dose of 600 mg/day).	Nausea, vomiting, diarrhea, and constipation are the most common GI adverse reactions observed with ribociclib; the majority of cases are mild to moderate. With dose modification and treatment, where indicated, these gastrointestinal events are reversible. Management of severe or intolerable events may require temporary dose interruption, reduction, or discontinuation of ribociclib. Recommendations for dose modification and management are provided in the label (SmPC).
Effects on the kidney In the 15- and 27-week rat toxicity studies, concurrent minimal degeneration and regeneration of kidney tubular epithelial cells occurred. The observed basophilic foci in these studies included piling up of epithelial cells and an increased nuclear to cytoplasmic volume ratio. This is considered indicative of a disturbance in normal tubular epithelial cell turnover. A closely-related CDK inhibitor was shown in rats to transiently arrest renal tubular cells in G0/G1, thereby reducing DNA damage and apoptosis following acute kidney injury (DiRocco et al 2014). The mixed presence of tubular epithelial degeneration and regeneration in ribociclib-treated rats; therefore, is most likely related to chronic low-level CDK4/6 inhibition and its effect on normal cellular turnover.	Cases of increased blood creatinine have been reported in clinical studies. Increase in creatinine may not be due to direct renal toxicity since ribociclib was shown to inhibit renal transporters (OCT2, MATE1) in vitro, which are involved in the active secretion of creatinine. In vitro, ribociclib inhibited renal transporters OCT2 (Ki: 1.90 µM) and MATE1 (Ki: 1.70 µM), which are involved in the active secretion of creatinine from the proximal tubules. The increase in creatinine may be due to inhibition of these transporters, rather than a result of direct renal toxicity of ribociclib. The endogenous marker, cystatin C, was measured to investigate this further. Cystatin C is not actively secreted by renal transporters, but rather is freely filtered by the renal glomeruli and may more accurately reflect renal function. No obvious changes in cystatin C levels were observed following a single 400 mg dose of ribociclib, suggesting ribociclib does not cause direct renal toxicity. These increases were usually fully reversible and presented as isolated low grade cases (grade 1-2) and did not result in renal failure. There is no data which suggests irreversible damage to the kidney.

	Dose modification and management guidelines for other toxicities and recommended dose modification for adverse drug reactions should be considered as recommended in the label.
Lung and mesenteric lymph node Increased alveolar macrophages in the lungs and histiocytosis in the lymph nodes were observed in all rat toxicity studies and in the 4-week dog toxicity study only. In the 4-week dog study, pulmonary inflammation with accumulation of alveolar macrophages/foam cells was considered to be related to the oral route of administration and resulting from inhalation of small droplets of the formulation deposited at the laryngeal orifice during the gavage procedure, or from inhalation of droplets of saliva upon excessive salivation or aspiration secondary to emesis. As obliterative bronchiolitis/organizing pneumonia is a rare complication in dogs dosed orally by gavage, this finding suggests an irritative potential of the formulated test-article if inhaled into the respiratory tract. This effect was not reproduced with more careful attention to dosing procedures in the 15- and 39-week dog toxicity study at same dose levels. The increased alveolar macrophages in the lungs and histiocytosis in the lymph nodes observed in rat toxicity studies was not progressive with long term exposure. All changes recovered or showed a trend towards reversibility.	The pulmonary findings seen in preclinical studies have no clear relevance to human use, as there is no increased risk of lung events. ILD/Pneumonitis is a class effect for CDK4/6 inhibitor. Cases of ILD/Pneumonitis have been reported with ribociclib in clinical studies and in the post-marketing setting. Dose modification and management guidance for ILD/Pneumonitis should be followed as recommended in the EU SmPC.
Effects on the bone and skin In dogs only treated for up to 4 weeks decreased bone formation and epidermal atrophy of the skin at the costochondral junction were observed. The decreased bone formation and atrophy of epidermis are most likely related to an inhibitory effect of ribociclib on proliferation of the growth plate chondrocytes in bones (Ogasawara et al 2011) and of keratinocytes in the basal layer of skin (Miliani de Marval et al 2001), respectively. These changes were fully reversed after a 4-week treatment-free period. In the 15- or 39-week dog toxicity studies with three weeks on one week off regimen, no epidermal atrophy or bone changes occurred. Neither bone nor skin effects occurred in rat studies with ribociclib.	No effect on bone or epidermis (atrophy) in humans has been observed. In clinical trials, rash (unrelated to epidermal atrophy) has been reported and was seen with a greater imbalance in ribociclib vs placebo treated patients but was mild in nature and reversible. Dose modification and management guidelines for other toxicities and recommended dose modification for adverse drug reactions should be considered as recommended in the label for severe or intolerable skin reactions (SmPC).
Carcinogenicity Ribociclib was assessed for carcinogenicity in a 2-year rat study.	Considering important differences between rodents and humans with regard to synthesis and role of prolactin (Ben-Jonathan et al 2008, Steinbach et al 2015),

Oral administration of ribociclib for 2 years resulted in an increased incidence of endometrial epithelial tumors and glandular and squamous hyperplasia in the uterus/cervix of female rats at doses ≥300 mg/kg/day as well as an increased incidence in follicular tumors in the thyroid glands of male rats at a dose of 50 mg/kg/day. Mean exposure at steady state (AUC0-24h) in female and male rats in whom neoplastic changes were seen was 1.2 and 1.4-fold that achieved in patients at the recommended dose of 600 mg/day, respectively. Mean exposure at steady state (AUC0-24h) in female and male rats in whom neoplastic changes were seen was 2.2- and 2.5-fold that achieved in patients at a dose of 400 mg/day, respectively. Additional non-neoplastic proliferative changes consisted of increased liver altered foci (basophilic and clear cell) and testicular interstitial (Leydig) cell hyperplasia in male rats at doses of ≥5 mg/kg/day and 50 mg/kg/day, respectively. The mechanism for the thyroid neoplastic findings in males was due to a rodent-specific microsomal enzyme induction in the liver resulting in increased incidence/severity of clear and basophilic foci in the liver and excess TSH secretion as a compensatory mechanism to increased thyroid hormone hepatic clearance. The effects in the male and female reproductive organs were related to a prolonged hypoprolactinemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis.	this mode of action is not expected to have consequences in humans. Any potential increase of estrogen/progesterone ratio in humans by this mechanism would be compensated by an inhibitory action of concomitant anti-estrogen therapy on estrogen synthesis as in humans. Kisqali is indicated in combination with estrogen-lowering agents. Novartis has updated the 'Non-clinical safety data' section of the SmPC, to reflect this new non-clinical safety information from the two-year carcinogenicity study in rats
Reproductive toxicity Ribociclib induced embryotoxicity and fetotoxocity in rats and rabbits and teratogenicity (malformations and external, visceral and skeletal variants) in rabbits. In a fertility study in female rats, ribociclib did not affect the reproductive function, fertility or early embryonic development at any dose up to 300 mg/kg/day (likely less or equal to patient's clinical exposure based on AUC at the highest recommended dose of 600 mg/day). Ribociclib has not been evaluated in male fertility studies. However, atrophic changes in testes were reported in rat and dog toxicity studies at exposures that were less than or equal to human exposure at the highest recommended daily dose of 600 mg/day based on AUC.	There is no clinical data available regarding effects of ribociclib on fertility. Based on animal studies, Kisqali may impair fertility in males of reproductive potential. Pregnancy status should be verified prior to starting treatment with Kisqali. Kisqali is not recommended during pregnancy and in women of childbearing potential not using contraception. Females of childbearing potential who are receiving Kisqali should use effective contraception (methods that result in <1% pregnancy rates) during therapy and for 3 weeks after stopping treatment with Kisqali. (SmPC).
Lactation Ribociclib and its metabolites readily passed into the milk of lactating rats. The exposure to ribociclib was higher in milk than in plasma.	It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breast-fed infant or the effects of ribociclib on milk

	production. Because of the potential for serious adverse reactions in nursing infants from ribociclib, a decision should be made whether to discontinue breast-feeding or discontinue ribociclib, taking into account the importance of the drug to the mother. It is recommended that women taking ribociclib should not breastfeed for at least 21 days after the last dose (SmPC).
Genotoxicity Based on in vitro and in vivo genotoxicity studies, ribociclib is considered to be non-genotoxic.	Based on the current available data, there is no concern relevant to human usage.
Phototoxicity The in vitro 3T3 Neutral Red Uptake phototoxicity profiling assay demonstrated no phototoxic potential for ribociclib.	Based on the current available data, there is no concern relevant to human usage.
General safety pharmacology	
Cardiovascular (including potential for QT interval prolongation) In vitro, inhibition of hERG activity observed for LEE011 (IC50=5.5 to 53 µM depending on the assay) and LEQ803 (metabolite of LEE011 accounting for ~10% of parent AUC in humans) (IC50=4.5 and 15.8 µM depending on the assay). In-vivo cardiac safety studies in dogs demonstrated a signal for QT prolongation at an exposure achieved in patients following the recommended dose of 600 mg with the potential to induce incidences of premature ventricular contraction (PVCs) at higher exposure levels (approximately 5-fold the clinical Cmax). There were no effects on heart rate, blood pressure, core body temperature, or other electrocardiogram (ECG) findings.	**Cardiovascular (including potential for QT interval prolongation)** Prolongation of the QTc interval has been observed with ribociclib in clinical studies. The effect on QT interval prolongation is concentration-dependent and reversible. No case of Torsades de Pointes has been reported in clinical trials. ECG and serum electrolytes monitoring should be done prior to and during treatment with ribociclib as recommended in the prescribing information. Dosage interruptions, adjustments or discontinuation should be considered in case of QT prolongation as per the prescribing information. (SmPC) Co-administration of ribociclib with drugs known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided and if treatment with strong CYP3A4 inhibitor cannot be avoided, dose reduction of ribociclib is recommended as per the prescribing information. When ribociclib is co-administered with other medicinal products, the SmPC of the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

	Treatment with ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation.
Nervous system Studies in the rat did not reveal any effects on the CNS (functional observations) after a single oral gavage administration of ribociclib at 200 mg/kg.	**Nervous system** Based on the current available data, there is no concern relevant to human usage.
Respiratory system Studies in the rat did not reveal any effects on respiratory functions (tidal volume, respiratory rate, minute volume) after a single oral gavage administration of ribociclib at 200 mg/kg.	**Respiratory system** Cases of ILD/Pneumonitis have been reported with ribociclib in clinical studies and in the post-marketing setting. Respiratory symptoms secondary to ILD/Pneumonitis can be observed. Recommendations to monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea are included in the EU SmPC.
Mechanisms for drug interactions	
Food: Ribociclib is classified as a biopharmaceutics classification system class IV compound, with slight pH dependent solubility and moderate permeability.	Food does not affect the pharmacokinetics (PK) of ribociclib administered as a drug-in-capsule formulation or as a tablet formulation based on results of food effect studies in healthy subjects. The prescribing information states ribociclib can be taken without regard to meals.
CYP3A4 substrates: In vitro, ribociclib was a reversible inhibitor of CYP1A2 (Ki,u: 13.0 µM), CYP2E1 (Ki,u: 24.5 µM), and CYP3A4/5 (Ki,u: 30.0 µM; Ki,u: 4.44 µM, kinact: 0.02 min^{-1}). No induction of CYP enzymes was observed in vitro.	Ribociclib is considered a moderate to strong CYP3A4 inhibitor based on clinical data and simulated data using physiologically-based PK (PBPK) models. Ribociclib did not have a substantial effect on CYP1A2 in humans. Ribociclib is also unlikely to result in clinical interactions with CYP2E1 substrates (Ki,u for CYP2E1 >Ki,u for CYP1A2). The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index may need to be reduced as ribociclib can increase their exposure. When ribociclib is co-administered with other medicinal products, the SmPC of the other products must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant administration of ribociclib with CYP3A4 substrates which may have serious and/or life-threatening adverse reactions should be avoided.

	This interaction is appropriately addressed in the label and therefore, not being considered as an important risk for ribociclib. (SCP)
CYP3A4 inducers and inhibitors: Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 (~63%) with a minor contribution by flavin-containing monooxygenase 3 (FMO3) (~16%). The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4.	Ribociclib exposure may be markedly affected by concurrent use of a strong CYP3A4 inhibitor or inducer. Drugs that are strong inhibitors or inducers of CYP3A4 should not be co-administered with ribociclib. If co-administration of ribociclib with strong CYP3A4 inhibitor cannot be avoided, dose reduction or interruption of ribociclib is recommended as per the prescribing information based on tolerability assessments. Co-administration with a strong CYP3A4 inhibitor should preferably not be long-term. Ribociclib dose interruption and/or reduction and close monitoring for adverse drug reactions (ADRs) are recommended until resolution of toxicity. Pomegranates or pomegranate juice, grapefruit or grapefruit juice all of which are known to inhibit cytochrome CYP3A4 enzymes and may increase the exposure to ribociclib should be avoided during treatment. This interaction is appropriately addressed in the label and therefore, not being considered as an important risk for ribociclib.
Effect of ribociclib on transporters	
OCT 1 and OATP1B1 OCT2 MATE1 and MATE2: Ribociclib inhibits transporter proteins in vitro, including OATPB1 (Ki: 33.4 uM), BCRP (IC50: 24.0 uM), OCT1 (Ki: 17.3 µM), OCT2 (1.90 µM), MATE1 (1.70 µM), MATE2K (31.0 µM), and BSEP (IC50: 4.7 µM).	At the therapeutic dose, clinical interactions with sensitive OCT1 as well as OATP1B1 substrates are unlikely to occur but cannot be completely excluded (Ki value 14-fold (OCT1) and 28-fold (OATP1B1) higher than Cmax,ss,u). Clinical interactions with sensitive substrates of OCT2 (Ki only ~1.6-fold higher than Cmax,ss,u) as well as of MATE1 (Ki ~1.4-fold higher than Cmax,ss,u) may occur. Inhibition of the renal uptake transporter MATE2K is unlikely at therapeutic ribociclib concentrations (Ki value is more than 25-fold higher than Cmax,ss,u). **P-gp, BCRP and BSEP** At the therapeutic dose, clinical interactions may occur with sensitive BCRP substrates.

	Ribociclib may inhibit systemic (Cmax, ss, u/Ki >0.02) as well as intestinal (Cgut/Ki >10) BCRP activity. The in vitro inhibition potential on P-gp is not anticipated to cause significant interactions clinically. The Ki value for BSEP inhibition is about 2-fold below the anticipated intrahepatic unbound ribociclib concentration indicating a potential for inhibition of canalicular bile salt efflux. Based on in vitro data, ribociclib may inhibit BCRP, OCT2 and MATE1, and human BSEP at clinically relevant concentrations. Caution and monitoring for toxicity is advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index.
Other toxicity-related information or data	
None	
Source: DiRocco et al 2014, Miliani et al 2001, Ogasawara et al 2011, Pietras et al 2011, SmPC, Summary of Clinical Pharmacology.	

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Overall, clinical trial exposure to ribociclib in patients with early and advanced breast cancer by duration of treatment, by age, race and region is summarized in this section.

4.1.1 HR-positive, HER2-negative early breast cancer

The safety analyses were based on patients/assessments included in the Safety Set of NATALEE (CLEE011O12301C) pivotal study.

Table 4-1 Study included in the combination therapy

Study	Population	Data cut-off date	Combination	Exposure
Ph III, multicenter, randomized, open-label study				
CLEE011O12301C (NATALEE)	Pre- or peri-menopausal women with HR+, HER2- early breast cancer	21-Jul-2023	Ribociclib 400 mg + (letrozole 2.5 mg or anastrozole 1 mg)	ET+RIBO (N=2525) ET only (N=2442)

Overall, a total of 2525 patients were exposed to ribociclib plus endocrine therapy (ET) and 2442 patients were exposed to ET only.

In the ribociclib plus ET group, 1287 out of 2525 patients received study treatment for ≥ 36 months (with a cumulative exposure corresponding to 6904.3 patient-years). The median duration of exposure to study treatment was 36.2 months (range: 0 to 54 months) (Table 4-2). A majority of the patients (1917 out of 2525 patients) were adults in the age range of ≥45 years, and 56 patients were in the age range of ≥75 years. (Table 4-4) Overall, patients were predominately White (1858 out of 2525 patients) (Table 4-5) and the majority of patients were from Europe (1488 out of 2525 patients) (Table 4-6).

Table 4-2 Duration of exposure to study treatment (Safety Set)

Adherence	ET+ Ribociclib N=2525	ET only N=2442
Duration of exposure		
0-<3 months	122 (4.8%)	167 (6.8%)
3-<6 months	84 (3.3%)	79 (3.2%)
6-<9 months	58 (2.3%)	50 (2.0%)
9-<12 months	48 (1.9%)	54 (2.2%)
12-<15 months	40 (1.6%)	45 (1.8%)
15-<18 months	33 (1.3%)	44 (1.8%)
18-< 21 months	45 (1.8%)	56 (2.3%)
21-<24 months	33 (1.3%)	35 (1.4%)
24-<27 months	25 (1.0%)	28 (1.1%)

27-<30 months	285 (11.3%)	259 (10.6%)
30-<33 months	124 (4.9%)	126 (5.2%)
33-<36 months	341 (13.5%)	290 (11.9%)
≥36 months	1287 (51.0%)	1209 (49.5%)
Duration of exposure		
n	2525	2442
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
Patient-years is calculated as the sum of exposure (in years) across all patients Source:Annex 7-Table 14.5-1.3		

Table 4-3 Duration of exposure by study treatment component (Safety set)

Adherence	**Ribociclib N=2525**	**NSAI N=4967**	
		ET+ Ribociclib N=2525	**ET only N=2442**
Duration of exposure			
0 - < 3 months	305 (12.1%)	126 (5.0%)	170 (7.0%)
3 - < 6 months	164 (6.5%)	85 (3.4%)	77 (3.2%)
6 - < 9 months	89 (3.5%)	56 (2.2%)	51 (2.1%)
9 - < 12 months	51 (2.0%)	47 (1.9%)	55 (2.3%)
12 - < 15 months	47 (1.9%)	39 (1.5%)	44 (1.8%)
15 - < 18 months	37 (1.5%)	36 (1.4%)	47 (1.9%)
18 - < 21 months	44 (1.7%)	44 (1.7%)	56 (2.3%)
21 - < 24 months	36 (1.4%)	35 (1.4%)	31 (1.3%)
24 - < 27 months	46 (1.8%)	26 (1.0%)	28 (1.1%)
27 - < 30 months	267 (10.6%)	293 (11.6%)	267 (10.9%)
30 - < 33 months	211 (8.4%)	113 (4.5%)	119 (4.9%)
33 - < 36 months	1205 (47.7%)	345 (13.7%)	301 (12.3%)
≥36 months	23 (0.9%)	1280 (50.7%)	1196 (49.0%)
Duration of exposure (months)			
n	2525	2525	2442
Mean	25.44	32.69	31.78

SD	13.157	12.856	13.677
Minimum	0.0	0.0	0.0
Median	32.9	36.0	35.9
Maximum	37.0	54	54
Patient-years	5352.1	6879.1	6467.5
Patient-year is calculated as the sum of exposure (in years) across all patients. Source: Annex 7-Table 14.5-1.4			

Table 4-4 Clinical trial exposure to study treatment, by age (Safety Set)

	ET+Ribociclib N=2525		ET Only N=2442	
Age group (years)	**Patients**	**Patient-years**	**Patients**	**Patient-years**
<45	608	1691.9	549	1435.4
≥45	1917	5212.4	1893	5051.9
<65	2123	5839.2	2091	5544.8
≥65	402	1065.1	351	942.5
<75	2469	6770.4	2379	6334.7
≥75	56	134.0	63	152.6

Patient-years is calculated as the sum of exposure (in years) across all patients.
Source: Annex 7-Table 14.5-1.1

Table 4-5 Clinical trial exposure to study treatment, by race (Safety Set)

	ET + Ribociclib N=2525		ET Only N=2442	
Race	**Patients**	**Patient-years**	**Patients**	**Patient-years**
White	1858	5116.4	1795	4838.8
Black or African American	41	118.3	43	104.8
American Indian or Alaska Native	4	13.2	3	11.3
Asian	340	943.4	313	799.0
Native Hawaiian or Other Pacific Islander	3	9.1	1	2.3
Other	144	355.8	162	397.7
Unknown	135	348.1	125	333.4

Patient-years is calculated as the sum of exposure (in years) across all patients.
Source: Annex 7-Table 14.5-1.1

Table 4-6 Clinical trial exposure to study treatment, by region (Safety Set)

	ET + Ribociclib N=2525		ET Only N=2442	
Region	**Patients**	**Patient-years**	**Patients**	**Patient-years**
Europe	1488	4154.0	1470	4075.3
North America/Australia	619	1590.0	560	1319.3
Asia	280	777.7	269	692.5
Latin America	138	382.6	143	400.3

Patient-years is calculated as the sum of exposure (in years) across all patients.
Source: Annex 7-Table 14.5-1.1

4.1.2 HR-positive, HER2-negative advanced breast cancer

The safety analyses were based on patients/assessments included in the Safety Set. The following studies were included in the combination safety pool to support the evaluation of benefit-risk in the advanced and metastatic breast cancer setting indication (Table 4-7).

Table 4-7 Studies included in combination therapy pool

Study	Population	Data cut-off date	Combination*	Exposure
Ph III randomized, double-blind, placebo-controlled studies				
Study E2301 (MONALEESA-7)	Pre- or peri-menopausal women with HR+, HER2- advanced breast cancer	29-Jun-2020	Ribociclib 600 mg/placebo + (letrozole 2.5 mg or anastrozole 1 mg) + goserelin 3.6 mg	RIBO+LET/ANA (N=248) PBO+LET/ANA (N=247)
Study A2301 (MONALEESA-2)	Post-menopausal women with HR+, HER2- advanced breast cancer	10-Jun-2021	Ribociclib 600 mg/placebo + letrozole 2.5 mg	RIBO+LET (N=334) PBO+LET (N=330)
Study F2301 (MONALEESA-3)	Men and Post-menopausal women with HR+, HER2- advanced breast cancer	30-Oct-2020	Ribociclib 600 mg/placebo + fulvestrant 500 mg	RIBO+FUL (N=483) PBO+FUL (N=241)

* Dosing regimens: ribociclib/placebo: once daily on Days 1-21 of a 28-day cycle; letrozole/ anastrozole: once daily; goserelin: once every 28 days; fulvestrant: once every 28 days with 1 additional dose on C1D15

Overall, in the combination safety pool, a total of 1065 patients were exposed to ribociclib plus endocrine therapy (ET) treatment (hereafter referred as ribociclib group), and 818 patients were on placebo plus ET treatment (hereafter referred as placebo group). In the ribociclib group, 541 out of 1065 patients received study treatment for ≥ 18 months (with a cumulative exposure corresponding to 1938.3patient-years). The median duration of exposure to study treatment was 19.22 months (range 0.0-84.6 months) and to placebo was shorter with an exposure of 12.94 months (range 0.5-85.6 months) (Table 4-8). A majority of the patients (971 out of 1065 patients) were adults in the age range of ≥40 years, and 100 patients were in the age range of ≥75 years. (Table 4-10) A higher number of Caucasians (814 out of 1065 patients) received the drug

compared to other races (Table 4-11) and the majority of patients were from Europe and Australia (602 out of 1065 patients) (Table 4-12).

Table 4-8 Duration of exposure to study treatment (Safety Set)

	Pool	
Duration of exposure (months)	**RIBO + ET N=1065**	**PBO + ET N=818**
Exposure categories -n(%)		
< 3	160 (15.0)	154 (18.8)
3-<6	93 (8.7)	79 (9.7)
6-<9	68 (6.4)	69 (8.4)
9-<12	87 (8.2)	81 (9.9)
12-<15	66 (6.2)	71 (8.7)
15-<18	50 (4.7)	45 (5.5)
>=18	541 (50.8)	319 (39.0)
Exposure		
Mean	25.49	19.31
SD	21.702	18.582
Median	19.22	12.94
Minimum	0.0	0.5
Maximum	84.6	85.6
Patient-years	2262	1316.4
- Study treatment includes any medication that is part of study treatment - N is the number of patients in the safety set - Patient-years is calculated as the sum of exposure (in years) across all patients Source: Annex-7 Table 3-2.1		

Table 4-9 Duration of exposure to ribociclib/placebo (Safety Set)

	Pool	
Duration of exposure (months)	**RIBO + ET N=1065**	**PBO + ET N=818**
Total number of patients received ribociclib/placebo	1063	816
Exposure categories -n (%)		
< 3	202 (19.0)	158 (19.3)
3-<6	110 (10.3)	87 (10.6)
6-<9	75 (7.0)	81 (9.9)
9-<12	78 (7.3)	63 (7.7)

Duration of exposure (months)	_Pool_ RIBO + ET N=1065	PBO + ET N=818
12-<15	54 (5.1)	71 (8.7)
15-<18	48 (4.5)	44 (5.4)
>=18	496 (46.6)	312 (38.1)
Exposure		
Mean	23.49	18.72
SD	21.736	18.347
Median	15.93	12.68
Minimum	0.0	0.2
Maximum	84.7	85.4
Patient-years	2081	1272.8

- N is the number of patients in the safety set
- Total number of patients received ribociclib/placebo is used as the denominator
- Patient-years is calculated as the sum of exposure (in years) across all patients

Source: Annex-7 Table 3-2.2

Table 4-10 Clinical trial exposure to study treatment, by age (Safety Set)

Age group (years)	Pool RIBO+ET N=1065		PBO+ET N=818	
	Patients	Patient-years	Patients	Patient-years
<40	94	210.1	84	112.0
>=40	971	2052.2	734	1204.5
<65	689	1493.8	561	862.3
>=65	376	768.5	257	454.2
<75	965	2060.9	750	1202.8
>=75	100	201.4	68	113.6

- Patient-years is calculated as the sum of exposure (in years) across all patients

Source: Annex-7 Table 4-1.3

Table 4-11 Clinical trial exposure to study treatment, by race (Safety Set)

Race	Pool RIBO+ET N=1065		PBO+ET N=818	
	Patients	Patient-years	Patients	Patient-years
Asian	155	359.0	125	193.5

	Pool			
	RIBO+ET N=1065		PBO+ET N=818	
Race	Patients	Patient-years	Patients	Patient-years
Black	17	30.8	15	16.6
Caucasian	814	1692.5	625	1014.1
Other	37	81.9	18	25.8
Unknown	42	98.1	35	66.4

- Patient-years is calculated as the sum of exposure (in years) across all patients.
Source: Annex-7 Table 4-1.3

Table 4-12 Clinical trial exposure to study treatment, by region (Safety Set)

	Pool			
	RIBO+ET N=1065		PBO+ET N=818	
Region [1]	Patients	Patient-years	Patients	Patient-years
Asia	139	332.5	109	165.4
Europe and Australia	602	1216.0	424	659.4
Latin America	36	72.5	30	66.3
North America	207	424.3	191	304.7
Other	81	217.1	64	120.7

Patient-years is calculated as the sum of exposure (in years) across all patients
[1] Asia: Hong Kong, India, Malaysia, S. Korea, Singapore, Taiwan, and Thailand; Europe and Australia: Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Ireland, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, and United Kingdom; Latin America: Argentina, Brazil, Colombia, and Mexico; North America: Canada and United States; Other: All other countries (Israel, Jordan, Lebanon, Russia, Saudi Arabia, South Africa, Turkey, and UAE).

Source: Annex-7 Table 4-1.3

4.1.3 Exposure in special populations

The effect of varying degrees of hepatic function impairment (mild, moderate, severe based on Child-Pugh classification) and renal function impairment (mild, moderate, severe, ESRD based on aGFR) on ribociclib exposure was assessed in non-cancer subjects (Study LEE011A2109), (Study LEE011A2116) and in cancer patients via the population PK approach.

The total number of hepatic impairment patients (Table 4-13) and renal impairment patients (Table 4-14) who were exposed to ribociclib are summarized below.

Table 4-13 Clinical trial exposure, by special population (Hepatic impairment)

		Advanced breast cancer	Early breast cancer
Population/Category	**Hepatic impairment (Non-cancer Subjects)[a]**	**Hepatic impairment (Cancer Subjects)[b]**	**Hepatic impairment (Cancer Subjects)**
Mild impairment	6	91	221
Moderate impairment	6	0	3
Severe impairment	6	0	0
Normal	12	535	2290

Source: Study LEE011A2109 CSR, Study LEE011E2301 SCS, SCS Study O12301C, Annex 7-Table14.1-2.1c
[a] [Study LEE011A2109]. This was a dedicated study involving Non-cancer Subjects.
[a] Hepatic impairment groups are based on Child-Pugh classification.
[b] Studies included for the subgroup analysis': RIBO + ET (Study E2301, Study A2301 and Study X2107)
[b] Hepatic impairment groups are based on National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria
[b] No specific subgroup analysis was performed in these patients in Study LEE011F2301

Table 4-14 Clinical trial exposure, by special population (Renal impairment)

		Advanced breast cancer	Early breast cancer
Population/Category	**Renal impairment (Non-cancer Subjects)***	**Renal impairment (Cancer Patients via the population PK approach)**	**Renal impairment (Cancer Subjects)**
Mild impairment	0	488	1009
Moderate impairment	0	113	72
Severe impairment	7	0	0
ESRD	3	0	0
Normal	7	438	1434

Source: [Study LEE011A2116], [Pop PK Report], SCS Study O12301C, Annex 7-Table14.1-2.1c
*Study LEE011A2116 was a dedicated study involving Non-cancer Subjects.
Renal impairment categories are based on estimated GFR as calculated using Cockcroft-Gault formula.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

Information presented in this section is based on clinical study protocols of both NATALEE and MONALEESA trials (MONALEESA-2, MONALEESA-3 and MONALEESA-7).

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnancy and lactating women	Reproductive toxicity was observed in the non-clinical setting in animals; Ribociclib caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below and 1.5 times the human clinical exposure based on area under the curve (AUC). Ribociclib and its metabolites passed readily into rat milk. The exposure to ribociclib was higher in milk than in plasma.	No	CDK4/6 inhibitors are believed to cause fetal toxicity. Ribociclib and its metabolites have readily passed into the milk of lactating rats, therefore it is believed that ribociclib could cause fetal harm when administered to a pregnant or lactating woman.
Patients with severe renal impairment	Data on these patients is currently limited, and historically these patients were excluded from the clinical development program.	No	Study CLEE011A2116 Part I was completed. An almost 2-fold increase in exposure (AUC) and a 50% increase in Cmax was observed in the severe renal impairment patients in comparison to patients with normal renal function. [CLEE011A2116 CSR]. The results from this completed study are reflected in the SmPC.
Patients receiving treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A4.	Ribociclib is primarily metabolized through CYP3A4 and concomitant use of strong inhibitors/inducers may alter ribociclib plasma exposure.	No	The prescribing information recommends that concomitant use of strong CYP3A4 strong inhibitors or inducers should be avoided with ribociclib and an alternative concomitant medication with less potential to inhibit CYP3A4 and with no or minimal potential to induce CYP3A4 should be considered. In patients with advanced or metastatic breast cancer, if a strong CYP3A4 inhibitor must be co-administered, the dose of Kisqali should be reduced to 400 mg once daily.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			Patients with advanced or metastatic breast cancer who have had their dose reduced to 400 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, should be monitored for adverse reactions. If necessary, a reduction of the Kisqali dose to 200 mg should be considered. Patients with advanced or metastatic breast cancer who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, should be monitored for adverse reactions. If necessary, treatment with Kisqali should be interrupted. In patients with early breast cancer, If a strong CYP3A4 inhibitor must be co-administered, patients should be monitored for adverse reactions and, if necessary, a reduction of Kisqali dose to 200 mg should be considered. Patients with early breast cancer who have had their dose reduced to 200 mg ribociclib daily, and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, should be monitored for adverse reactions. If necessary, treatment with Kisqali should be interrupted. (SmPC). If the strong inhibitor is discontinued, ribociclib dose should be resumed to the dose used prior to the initiation of the strong CYP3A4 inhibitor after at least five half-lives of the strong CYP3A4 inhibitor. (SmPC).
Patients receiving drugs with narrow therapeutic windows	Ribociclib (400 mg) is a moderate inhibitor of CYP3A4 activity and is predicted to be a strong CYP3A4 inhibitor	No	Prescribing information recommends caution when ribociclib is administered with CYP3A4 substrates with a narrow therapeutic index. The dose of a sensitive

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
predominantly metabolized through CYP3A4/5.	(predicted 5.17-fold increase in midazolam AUC) at the clinically relevant dose of 600 mg based on simulations using PBPK models. Therefore, co-administration with ribociclib of drugs with narrow therapeutic windows that are CYP3A4/5 substrates is prohibited.		CYP3A4 substrate with a narrow therapeutic index should be reduced as ribociclib can increase its exposure. When ribociclib is co-administered with other medicinal products, the SmPC of the other products must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of ribociclib with CYP3A4 substrates which may have serious and/or life-threatening adverse reactions should be avoided (SmPC).
Co-administration of ribociclib with drugs known to have a risk of QT prolongation or induce Torsades de Pointes	Conservative approach was adopted in ribociclib clinical trials including the registration study, particularly for drugs with known risk of QT prolongation and narrow therapeutic window and/or metabolized through CYP3A4 given potential interaction with ribociclib, and serious events.	No	Prescribing information recommends monitoring of ECG and serum electrolytes prior to and during treatment with ribociclib, and as clinically indicated. Dosage modification and management should be considered in case of QT prolongation. Co-administration of ribociclib with drugs known to have a risk of QT prolongation and strong CYP3A4 inhibitors with a possible risk of QT prolongation should be avoided. If treatment with strong CYP3A4 inhibitors cannot be avoided, dose reduction or interruption of ribociclib is recommended as per the prescribing information based on tolerability assessments. Treatment with ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation (SmPC).
History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry.	These are precautionary measures to preclude enrolling patients with relevant cardiac disorders in clinical studies who might be placed at a higher risk of	No	Ribociclib has not been studied in patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, CHF, unstable angina or clinically significant bradycardia) and therefore, caution should be

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of documented congestive heart failure (New York Heart Association functional classification III-IV)	developing QT prolongation.		exercised in patients with relevant cardiac disorders. Treatment with ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients with: • Long QT syndrome • Uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias • Uncorrected electrolyte abnormalities
Documented cardiomyopathy			
Patient has a Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)			
History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months.			
On screening, any of the following cardiac parameters: bradycardia (heart rate <50 at rest), tachycardia (heart rate >90 at rest), PR interval >220 ms, QRS interval			

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
>109 ms, or QTcF >450 ms. Systolic blood pressure >160 or <90 mmHg.			

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Limited exposure in patients with hepatic and renal impairment. (Table 4-13), (Table 4-14) Patients with cardiovascular impairment were not included in the clinical development program
Population with relevant different ethnic origin	Patients of different racial and/or ethnic origins were included in the clinical development program. (Table 4-6, Table 4-12)
Subpopulations carrying relevant genetic polymorphisms	There were no studies in subpopulations carrying relevant genetic polymorphisms
Other	
Elderly patients (≥ 65 years)	Included in the clinical development program. (Table 4-4, Table 4-10)
Pediatric patients (<18 years of age)	Not included in the clinical development program

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in kilograms (kg) of active substance sold during the reporting interval and the Defined Daily Dose (DDD). The DDD for ribociclib is 450 mg, based on a targeted therapeutic daily dose of 600 mg in advanced/metastatic breast cancer during a treatment period of 21 days, followed by a period of seven days off treatment for every treatment cycle of 28 days.

6.1.2 Part II Module SV.1.2. Exposure

The estimated exposure for current approved indication of HR-positive, HER2-negative advanced and metastatic breast cancer is provided in Table 6-1 below.

Table 6-1 Estimated post-marketing (non-clinical trial) exposure

Formulation	Cumulative (Until 12-Mar-2023)	
	Amount sold (Kg)	Estimated exposure (PTY)
Kisqali FCT 200 mg	20,946.5	127,528

Source: Kisqali PSUR (Reporting Period: 13-Mar-2022 to 12-Mar-2023)
This table includes cumulative data obtained from IBD (13-Mar-2017 to Feb-2023).

As Kisqali is currently authorized in pre and post-menopausal women in EU and the only available formulation is 200mg tablet, no breakdown by age, gender or formulation is presented.

Table 6-2 Distribution of estimated post-marketing exposure by region (in patient treatment years)

Formulation	Period	EEA	USA and Canada	Japan	ROW*
Kisqali FCT 200 mg	Cumulative Until 12 Mar 2023	50,139.5	13,141.1	-	64,248

Source: Kisqali PSUR (Reporting Period: 13-Mar-2022 to 12-Mar-2023)
Source of data: Worldwide sales volume.
This table includes cumulative data obtained from IBD (13-Mar-2017 to Feb 2023).
The sum up values may not match the total, as the figures are rounded off.

*Note: Sales originating from United Kingdom is presented under ROW.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

A possible risk of misuse or dependence on ribociclib is not anticipated based on its mechanism of action and lack of psychopharmacologic effects. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged that would suggest a potential for abuse or dependence with ribociclib. Given the pattern of side effects and given the absence of effects that could lead to dependence, there is no known potential for abuse of ribociclib.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable, the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There are no changes to the safety concerns in this RMP update.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Incidences of adverse events related to each risk are presented in separate tables by indication. Details on the characterization of each risk are presented in the same table.

8.3.1.1 Important Identified Risk: Myelosuppression

Table 8-1 Incidence of Myelosuppression - HR-positive, HER2-negative early breast cancer (safety set)

	CLEE011O12301C (NATALEE)		
AESI category	ET + Ribociclib N=2525 n(%) (95% CI)	ET Only N=2442 n(%) (95% CI)	RD ET + Ribociclib vs. ET Only (95% CI)
Incidence of Myelosuppression – Anaemia			
ALL AEs	216 (8.6) (7.5, 9.7)	78 (3.2) (2.5, 4.0)	5.4 (4.1, 6.7)
CTC grade ≥3 AEs	8 (0.3) (0.1, 0.6)	8 (0.3) (0.1, 0.6)	0.0 (-0.3, 0.3)
AEs related to study treatment (Ribociclib and/or ET)	166 (6.6) (5.6, 7.6)	24 (1.0) (0.6, 1.5)	5.6 (4.5, 6.6)
AEs related to Ribociclib	165 (6.5) (5.6, 7.6)	0	6.5 (5.6, 7.5)
AEs related to ET	12 (0.5) (0.2, 0.8)	24 (1.0) (0.6, 1.5)	-0.5 (-1.0, 0.0)
AE requiring dose adjustment	1 (<0.1) (0.0, 0.2)	0	0.0 (0.0, 0.1)
AE requiring dose interruption	10 (0.4) (0.2, 0.7)	1 (<0.1) (0.0, 0.2)	0.4 (0.1, 0.6)

	CLEE011O12301C (NATALEE)		
AESI category	**ET + Ribociclib N=2525 n(%) (95% CI)**	**ET Only N=2442 n(%) (95% CI)**	**RD ET + Ribociclib vs. ET Only (95% CI)**
AE requiring dose adjustment or interruption	11 (0.4) (0.2, 0.8)	1 (<0.1) (0.0, 0.2)	0.4 (0.1, 0.7)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	2 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.2)
AEs leading to treatment discontinuation of Ribociclib	2 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.2)
AEs leading to treatment discontinuation of ET	0	0	
SAEs	3 (0.1) (0.0, 0.3)	3 (0.1) (0.0, 0.4)	0.0 (-0.2, 0.2)
On-treatment deaths	0	0	
Incidence of Myelosuppression - Leukopenia			
ALL AEs	595 (23.6) (21.9, 25.3)	111 (4.5) (3.8, 5.4)	19.0 (17.2, 20.9)
CTC grade ≥3 AEs	202 (8.0) (7.0, 9.1)	10 (0.4) (0.2, 0.8)	7.6 (6.5, 8.7)
AEs related to study treatment (Ribociclib and/or ET)	569 (22.5) (20.9, 24.2)	38 (1.6) (1.1, 2.1)	21.0 (19.3, 22.7)
AEs related to Ribociclib	569 (22.5) (20.9, 24.2)	0	22.5 (20.9, 24.2)
AEs related to ET	55 (2.2) (1.6, 2.8)	38 (1.6) (1.1, 2.1)	0.6 (-0.1, 1.4)
AE requiring dose adjustment	45 (1.8) (1.3, 2.4)	0	1.8 (1.3, 2.3)
AE requiring dose interruption	160 (6.3) (5.4, 7.4)	0	6.3 (5.4, 7.3)
AE requiring dose adjustment or interruption	169 (6.7) (5.7, 7.7)	0	6.7 (5.7, 7.7)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	6 (0.2) (0.1, 0.5)	0	0.2 (0.0, 0.4)
AEs leading to treatment discontinuation of Ribociclib	6 (0.2) (0.1, 0.5)	0	0.2 (0.0, 0.4)
AEs leading to treatment discontinuation of ET	0	0	
SAEs	0	0	
On-treatment deaths	0	0	
Incidence of Myelosuppression – Neutropenia			
ALL AEs	1579 (62.5) (60.6, 64.4)	113 (4.6) (3.8, 5.5)	57.9 (55.8, 60.0)

	CLEE011O12301C (NATALEE)		
AESI category	**ET + Ribociclib N=2525 n(%) (95% CI)**	**ET Only N=2442 n(%) (95% CI)**	**RD ET + Ribociclib vs. ET Only (95% CI)**
CTC grade ≥3 AEs	1118 (44.3) (42.3, 46.2)	22 (0.9) (0.6, 1.4)	43.4 (41.4, 45.3)
AEs related to study treatment (Ribociclib and/or ET)	1561 (61.8) (59.9, 63.7)	34 (1.4) (1.0, 1.9)	60.4 (58.5, 62.4)
AEs related to Ribociclib	1560 (61.8) (59.9, 63.7)	0	61.8 (59.9, 63.7)
AEs related to ET	145 (5.7) (4.9, 6.7)	34 (1.4) (1.0, 1.9)	4.4 (3.3, 5.4)
AE requiring dose adjustment	358 (14.2) (12.8, 15.6)	0	14.2 (12.8, 15.5)
AE requiring dose interruption	1093 (43.3) (41.3, 45.2)	3 (0.1) (0.0, 0.4)	43.2 (41.2, 45.1)
AE requiring dose adjustment or interruption	1099 (43.5) (41.6, 45.5)	3 (0.1) (0.0, 0.4)	43.4 (41.5, 45.3)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	28 (1.1) (0.7, 1.6)	0	1.1 (0.7, 1.5)
AEs leading to treatment discontinuation of Ribociclib	28 (1.1) (0.7, 1.6)	0	1.1 (0.7, 1.5)
AEs leading to treatment discontinuation of ET	3 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.3)
SAEs	2 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.2)
On-treatment deaths	0	0	
Incidence of Myelosuppression – Thrombocytopenia			
ALL AEs	162 (6.4) (5.5, 7.4)	56 (2.3) (1.7, 3.0)	4.1 (3.0, 5.2)
CTC grade ≥3 AEs	6 (0.2) (0.1, 0.5)	3 (0.1) (0.0, 0.4)	0.1 (-0.1, 0.4)
AEs related to study treatment (Ribociclib and/or ET)	146 (5.8) (4.9, 6.8)	23 (0.9) (0.6, 1.4)	4.8 (3.9, 5.8)
AEs related to Ribociclib	144 (5.7) (4.8, 6.7)	0	5.7 (4.8, 6.6)
AEs related to ET	12 (0.5) (0.2, 0.8)	23 (0.9) (0.6, 1.4)	-0.5 (-0.9, 0.0)
AE requiring dose adjustment	2 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.2)
AE requiring dose interruption	20 (0.8) (0.5, 1.2)	1 (<0.1) (0.0, 0.2)	0.8 (0.4, 1.1)
AE requiring dose adjustment or interruption	20 (0.8) (0.5, 1.2)	1 (<0.1) (0.0, 0.2)	0.8 (0.4, 1.1)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	1 (<0.1) (0.0, 0.2)	0	0.0 (0.0, 0.1)

	CLEE011O12301C (NATALEE)		
AESI category	**ET + Ribociclib N=2525 n(%) (95% CI)**	**ET Only N=2442 n(%) (95% CI)**	**RD ET + Ribociclib vs. ET Only (95% CI)**
AEs leading to treatment discontinuation of Ribociclib	1 (<0.1) (0.0, 0.2)	0	0.0 (0.0, 0.1)
AEs leading to treatment discontinuation of ET	0	0	
SAEs	0	0	
On-treatment deaths	0	0	

RD: Risk difference

Patients with multiple events in a grouping are counted only once in the grouping.

MedDRA Version 26.0 and eCRS dated 26-Aug-2023 have been used for reporting.

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.

Source: Annex 7-Table 14.5-2.3c, Annex 7-Table 14.5-2.3d, Annex 7-Table 14.5-2.3e and Annex 7-Table 14.5-2.3f.

Table 8-2 Incidence of Myelosuppression- HR-positive, HER2-negative advanced breast cancer (Safety Set)

AESI category	Pool		RD RIBO + ET vs. PBO + ET (95% CI)
	RIBO + ET N=1065 n (%) (95% CI)	PBO + ET N=818 n (%) (95% CI)	
Incidence of Myelosuppression – Anaemia			
ALL AEs	228 (21.4) (19.0, 24.0)	69 (8.4) (6.6, 10.6)	13.0 (9.9, 16.1)
CTC grade 3/4 AEs	41 (3.8) (2.8, 5.2)	18 (2.2) (1.3, 3.5)	1.6 (0.1, 3.2)
Related AEs	175 (16.4) (14.3, 18.8)	36 (4.4) (3.1, 6.0)	12 (9.4, 14.7)
AE requiring dose adjustment	5 (0.5) (0.2, 1.1)	0	0.5 (0.1, 0.9)
AE requiring dose interruption	28 (2.6) (1.8, 3.8)	7 (0.9) (0.3, 1.8)	1.8 (0.6, 2.9)
AEs leading to discontinuation	0	0	-
SAEs	12 (1.1) (0.6, 2.0)	3 (0.4) (0.1, 1.1)	0.8 (0.0, 1.5)
On-treatment deaths	0	0	-
Incidence of Myelosuppression – Neutropenia			
ALL AEs	806 (75.7) (73.0, 78.2)	56 (6.8) (5.2, 8.8)	68.8 (65.7, 71.9)
CTC grade 3/4 AEs	666 (62.5) (59.5, 65.5)	20 (2.4) (1.5, 3.8)	60.1 (57.0, 63.2)
Related AEs	795 (74.6) (71.9, 77.2)	48 (5.9) (4.4, 7.7)	68.8 (65.7, 71.8)
AE requiring dose adjustment	275 (25.8) (23.2, 28.6)	2 (0.2) (0.0, 0.9)	25.6 (22.9, 28.2)
AE requiring dose interruption	605 (56.8) (53.8, 59.8)	11 (1.3) (0.7, 2.4)	55.5 (52.4, 58.5)
AEs leading to discontinuation	11 (1.0) (0.5, 1.8)	0	1.0 (0.4, 1.6)
SAEs	26 (2.4) (1.6, 3.6)	1 (0.1) (0.0, 0.7)	2.3 (1.4, 3.3)
On-treatment deaths	0	0	-
Incidence of Myelosuppression – Leukopenia			
ALL AEs	372 (34.9) (32.1, 37.9)	38 (4.6) (3.3, 6.3)	30.3 (27.1, 33.5)
CTC grade 3/4 AEs	210 (19.7) (17.4, 22.2)	9 (1.1) (0.5, 2.1)	18.6 (16.1, 21.1)
Related AEs	354 (33.2) (30.4, 36.2)	29 (3.5) (2.4, 5.1)	29.7 (26.6, 32.8)
AE requiring dose adjustment	26 (2.4) (1.6, 3.6)	0	2.4 (1.5, 3.4)

AE requiring dose interruption	116 (10.9) (9.1, 12.9)	1 (0.1) (0.0, 0.7)	10.8 (8.9, 12.7)
AEs leading to discontinuation	1 (0.1) (0.0, 0.5)	0	0.1 (-0.1, 0.3)
SAEs	3 (0.3) (0.1, 0.8)	0	0.3 (0.0, 0.6)
On-treatment deaths	0	0	-
Incidence of Myelosuppression – Thrombocytopenia			
ALL AEs	105 (9.9) (8.1, 11.8)	15 (1.8) (1.0, 3.0)	8.0 (6.0, 10.0)
CTC grade 3/4 AEs	9 (0.8) (0.4, 1.6)	2 (0.2) (0.0, 0.9)	0.6 (0.0, 10.0)
Related AEs	96 (9.0) (7.4, 10.9)	7 (0.9) (0.3, 1.8)	8.2 (6.3, 10.0)
AE requiring dose adjustment	7 (0.7) (0.3, 1.3)	0	0.7 (0.2, 1.1)
AE requiring dose interruption	17 (1.6) (0.9, 2.5)	0	1.6 (0.8, 2.3)
AEs leading to discontinuation	0	1 (0.1) (0.0, 0.7)	-0.1 (-0.4, 0.1)
SAEs	5 (0.5) (0.2, 1.1)	1 (0.1) (0.0, 0.7)	0.3 (-0.1, 0.8)
On-treatment deaths	0	0	-
Incidence of Myelosuppression – Other*			
ALL AEs	4 (0.4) (0.1, 1.0)	0	0.4 (0.0, 0.7)
CTC grade 3/4 AEs	2 (0.2) (0.0, 0.7)	0	0.2 (-0.1, 0.4)
Related AEs	4 (0.4) (0.1, 1.0)	0	0.4 (0.0, 0.7)
AE requiring dose adjustment	0	0	-
AE requiring dose interruption	3 (0.3) (0.1, 0.8)	0	0.3 (0.0, 0.6)
AEs leading to discontinuation	0	0	-
SAEs	3 (0.3) (0.1, 0.8)	0	0.3 (0.0, 0.6)
On-treatment deaths	0	0	-

RD: Risk difference.
Patients with multiple events in a grouping are counted only once in the grouping.
MedDRA Version 24.0 and eCRS dated 16-Jun-2021 have been used for reporting.
Source: Annex-7 Table 4-2.14d, Table 4-2.14e, Table 4-2.14f, Table 4-2.14g, Table 4-2.14h.

RD: Risk difference.
Patients with multiple events in a grouping are counted only once in the grouping.
MedDRA Version 24.0 and eCRS dated 16-Jun-2021 have been used for reporting.
Source: Annex-7 Table 4-2.14d, Table 4-2.14e, Table 4-2.14f, Table 4-2.14g, Table 4-2.14h

Table 8-3 Myelosuppression: Other details

Name of the risk	Myelosuppression
Potential mechanisms	Myelosuppression is suggestive of direct effect of the compound on hematopoiesis and may be related to the pharmacological inhibition of cell replication due to CDK4/6 inhibition.
Evidence source(s) and strength of evidence	Bone marrow hypocellularity was predicted by preclinical studies and is considered to be related to the pharmacological inhibition of cell replication due to CDK4/6 inhibition.
Characterization of the risk:	Bone marrow suppression manifested with neutropenia, leukopenia, anemia, and/or thrombocytopenia observed in these studies is a known class effect observed with ribociclib treatment. **CLEE011O12301C (NATALEE)- HR-positive, HER2-negative early breast cancer (Table 8-1)** **Anemia:** • Higher incidences of anemia grouped AEs, including grade 3 and 4 events were observed in the ribociclib plus ET group (8.6% all grades, and 0.3% ≥ grade 3) relative to the ET only group (3.2% all grades, and 0.3% ≥ grade 3). The AEs suspected to be study drug related were reported in 6.6% in ribociclib plus ET group and 1.0% in ET only group. • Patients with anemia in the ribociclib plus ET group were managed with either dose adjustment (<0.1%) or interruption (0.4%). • Two patients (0.1%) in the ribociclib plus ET group and none in ET only group discontinued study treatment due to anemia. • Three patients (0.1%) in the ribociclib plus ET group and 3 (0.1%) patients in the ET only group had anemia events considered SAEs. • No on-treatment deaths were reported in both the treatment groups. **Neutropenia:** • Higher incidences of neutropenia grouped AEs, including grade 3 and 4 events were observed in the ribociclib plus ET group (62.5% all grades, and 44.3% ≥ grade 3) relative to the ET only group (4.6% all grades, and 0.9% ≥ grade 3). The AEs suspected to be study drug related were reported in 61.8% in ribociclib plus ET group and 1.4% in ET only group. • Rare incidences of Febrile neutropenia were reported in 7 (0.3%) patients in ribociclib plus ET group and none in ET only group (CLEE011O12301C CSR) and (iDFS analysis efficacy and safety update). • Patients with neutropenia in the ribociclib plus ET group were mainly managed with either dose adjustment (14.2%) or dose interruption (43.3%). • Study treatment was discontinued for 28 patients (1.1%) in the ribociclib plus ET group and none in ET only group. • Two patients (0.1%) in the ribociclib plus ET group had neutropenia events considered SAEs. No SAEs were reported in ET only group. • No on-treatment deaths were reported in both the treatment groups. **Leukopenia** • Higher incidences of leukopenia grouped AEs, including grade 3 and 4 events were observed in the ribociclib plus ET group (23.6% all grades,

Name of the risk	Myelosuppression
	and 8.0% ≥ grade 3) relative to the ET only group (4.5% all grades, and 0.4% ≥ grade 3).The AEs suspected to be study drug related were reported in 22.5% in ribociclib plus ET group and 1.6% in ET only group. • Patients with leukopenia in the ribociclib plus ET group were managed with either dose adjustment (1.8%) or interruption (6.3%). • Six patients (0.2%) in the ribociclib plus ET group and none in ET only group discontinued study treatment due to an event of leukopenia. • No SAEs or on-treatment deaths were reported in both the treatment groups. **Thrombocytopenia:** • Thrombocytopenia grouped AEs were reported more frequently in the ribociclib plus ET group (6.4% all grades and, 0.2% ≥ grade 3) relative to the ET only group (2.3% all grades; 0.1% ≥ grade 3). The AEs suspected to be study drug related were reported in 5.8% in ribociclib plus ET group and 0.9% in ET only group. • Patients with thrombocytopenia in the ribociclib plus ET group were managed with either dose adjustment (0.1%) or interruption (0.8%). • One patient (<0.1%) in the ribociclib plus ET group and none in ET only group discontinued study treatment due to thrombocytopenia. • No SAEs or on-treatment deaths were reported in both treatment groups. There was no patient who presented an event that belonged to the Myelosuppression: other AESI (Haematopoietic cytopenias affecting more than one type of blood cell SMQ Narrow) (SCS Study O12301C). **HR-positive, HER2-negative advanced breast cancer - Pooled Data set: (Study E2301 – [NSAI], Study F2301, Study A2301)** **Anemia:** • Higher incidences of anemia grouped AEs, including grade 3 and 4 events, were observed in the ribociclib (21.4% all grades, and 3.8% grade 3/4) relative to the placebo group (8.4% all grades, and 2.2% grade 3/4). Most of these events were suspected to be study drug related (16.4% and 4.4%). • Patients with anemia in the ribociclib group were mainly managed with either dose adjustment (0.5%) or interruption (2.6%). None of the patients in either treatment group discontinued study treatment due to anemia. • Twelve patients (1.1%) in the ribociclib group and three patients (0.4%) in the placebo group had anemia events considered as a SAE. • No on treatment deaths were reported in both the treatment groups. • Exposure-adjusted incidence rates for anemia grouped AEs were 12.3 / 100 PTY in ribociclib group and 5.5 / 100 PTY in placebo group. **Neutropenia**: • Higher incidences of neutropenia grouped AEs, including grade 3 and 4 events, were observed in the ribociclib (75.7% all grades, and 62.5% grade 3/4) relative to the placebo group (6.8% all grades, and 2.4% grade 3/4). Most of these events were suspected to be study drug related (74.6% and 5.9%).

Name of the risk	Myelosuppression
	• Patients with neutropenia in the ribociclib group were mainly managed with either dose adjustment (25.8%) or interruption (56.8%). • Fewer SAEs were reported in patients in both the ribociclib (2.4%) and the placebo (0.1%) groups. Eleven patients (1.0%) in the ribociclib group discontinued due to an event of neutropenia. • No on treatment deaths were reported in both the treatment groups. • Exposure-adjusted incidence rates for neutropenia grouped AEs were 144.8 / 100 PTY in ribociclib group and 4.5 / 100 PTY in placebo group. **Leukopenia:** • Higher incidences of leukopenia grouped AEs, including grade 3 and 4 events, were observed in the ribociclib (34.9% all grades, and 19.7% grade 3/4) relative to the placebo group (4.6% all grades, and 1.1% grade 3/4). Most of these events were suspected to be study drug related (33.2% and 3.5%). • Patients with leukopenia in the ribociclib group were managed with either dose adjustment (2.4%) or interruption (10.9%). One patient (0.1%) in the ribociclib group discontinued study treatment due to an event of leukopenia. • Fewer SAEs were reported in patients in the ribociclib group (0.3%) and none in the placebo group. • No on treatment deaths were reported in both the treatment groups. • Exposure-adjusted incidence rates for leukopenia grouped AEs were 24.6 / 100 PTY in ribociclib group and 3.1 / 100 PTY in placebo group. **Thrombocytopenia:** • Thrombocytopenia grouped AEs were reported more frequently in the ribociclib group (9.9% all grades; 0.8% grade 3/4) compared to the placebo group (1.8% all grades; 0.9% grade 3/4), with majority of the cases (9.0% vs.0.2%) being suspected to be related to study treatment. • Patients with thrombocytopenia in the ribociclib group were managed with either dose adjustment (0.7%) or interruption (1.6%). One patient in the placebo group discontinued study treatment due to thrombocytopenia. • Five SAEs were reported in patients in the ribociclib group (0.5%) and one (0.1%) in the placebo group. • No on treatment deaths were reported in both the treatment groups. • Exposure-adjusted incidence rates for thrombocytopenia grouped AEs were 5.1 / 100 PTY in ribociclib group and 1.2 / 100 PTY in placebo group. **Myelosuppression-Other cytopenias:** • This category includes, hematopoietic cytopenias affecting more than one type of blood cell. • AEs were reported only in the ribociclib group (0.4% all grades; 0.2% grade 3/4), and all the cases were suspected to be related to study treatment. • Three SAEs were reported in patients in the ribociclib (0.3%) group. • These events were managed with dose interruption (0.3%). No on treatment deaths were reported in both the treatment groups.

Name of the risk	**Myelosuppression**
	• Exposure-adjusted incidence rates for Myelosuppression-Other grouped AEs were 0.2 / 100 PTY in ribociclib group.
Risk factors and risk groups	Patients with low baseline neutrophil and/or leukocyte counts are at a risk.
Preventability	To mitigate the risk of severe myelosuppression, peripheral blood cell counts should be monitored in patients receiving ribociclib treatment. A complete blood count should be performed before initiating ribociclib, every 2 weeks for the first 2 treatment cycles with ribociclib, at the beginning of each of the subsequent 4 treatment cycles then as clinically indicated, or as specified in each study protocol. Physicians should instruct patients to promptly report any fever during the treatment with ribociclib. Current text in the SmPC (Section 4.2, Section 4.4 and Section 4.8) addresses the risk in the patient population.
Impact on the benefit-risk balance of the product	Moderate impact due to the risk of complications associated to myelosuppression including infections.
Public health impact	With dose modification and management where indicated, the public health concern is low.

8.3.1.2 Important identified risk: Hepatobiliary toxicity

Table 8-4 Incidence of Hepatobiliary toxicity- HR-positive, HER2-negative early breast cancer (Safety Set)

	CLEE011O12301C (NATALEE)		
AESI category	**ET + Ribociclib N=2525 n(%) (95% CI)**	**ET Only N=2442 n(%) (95% CI)**	**RD ET + Ribociclib vs. ET Only (95% CI)**
ALL AEs	667 (26.4) (24.7, 28.2)	273 (11.2) (10.0, 12.5)	15.2 (13.1, 17.4)
CTC grade ≥3 AEs	217 (8.6) (7.5, 9.8)	42 (1.7) (1.2, 2.3)	6.9 (5.7, 8.1)
AEs related to study treatment (Ribociclib and/or ET)	553 (21.9) (20.3, 23.6)	108 (4.4) (3.6, 5.3)	17.5 (15.7, 19.3)
AEs related to Ribociclib	541 (21.4) (19.8, 23.1)	0	21.4 (19.8, 23.0)
AEs related to ET	130 (5.1) (4.3, 6.1)	108 (4.4) (3.6, 5.3)	0.7 (-0.5, 1.9)
AE requiring dose adjustment	66 (2.6) (2.0, 3.3)	0	2.6 (2.0, 3.2)
AE requiring dose interruption	313 (12.4) (11.1, 13.7)	10 (0.4) (0.2, 0.8)	12.0 (10.7, 13.3)
AE requiring dose adjustment or interruption	314 (12.4) (11.2, 13.8)	10 (0.4) (0.2, 0.8)	12.0 (10.7, 13.3)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	225 (8.9) (7.8, 10.1)	3 (0.1) (0.0, 0.4)	8.8 (7.7, 9.9)
AEs leading to treatment discontinuation of Ribociclib	223 (8.8) (7.8, 10.0)	0	8.8 (7.7, 9.9)
AEs leading to treatment discontinuation of ET	25 (1.0) (0.6, 1.5)	3 (0.1) (0.0, 0.4)	0.9 (0.5, 1.3)
SAEs	26 (1.0) (0.7, 1.5)	5 (0.2) (0.1, 0.5)	0.8 (0.4, 1.3)
On-treatment deaths	0	0	

Notable hepatic values (Safety Set)		
	Ribociclib + ET N=2525 n/m (%)	**ET only N=2442 n/m (%)**
AST		
> 3*ULN	237/2498 (9.5%)	65/2381 (2.7%)
> 5*ULN	133/2499 (5.3%)	26/2381 (1.1%)
> 8*ULN	88/2499 (3.5%)	6/2381 (0.3%)
> 10*ULN	65/2499 (2.6%)	4/2381 (0.2%)
> 20*ULN	20/2499 (0.8%)	0/2381 (0%)
ALT		
> 3*ULN	344/2505 (13.7%)	80/2381 (3.4%)

> 5*ULN	205/2505 (8.2%)	25/2382 (1.0%)
> 8*ULN	127/2505 (5.1%)	6/2383 (0.3%)
> 10*ULN	100/2505 (4.0%)	2/2383 (0.1%)
> 20*ULN	38/2505 (1.5%)	1/2383 (<0.1%)
ALT or AST		
> 3*ULN	364/2505 (14.5%)	105/2384 (4.4%)
> 5*ULN	212/2505 (8.5%)	42/2384 (1.8%)
> 8*ULN	140/2505 (5.6%)	11/2384 (0.5%)
> 10*ULN	108/2505 (4.3%)	5/2384 (0.2%)
> 20*ULN	40/2505 (1.6%)	1/2384 (<0.1%)
TBILI		
> ULN	214/2474 (8.6%)	187/2337 (8.0%)
> 2*ULN	18/2504 (0.7%)	12/2383 (0.5%)
> 3*ULN	10/2505 (0.4%)	1/2385 (<0.1%)
ALP		
> 1.5*ULN	133/2470 (5.4%)	151/2356 (6.4%)
> 2*ULN	55/2491 (2.2%)	56/2374 (2.4%)
> 3*ULN	16/2495 (0.6%)	17/2376 (0.7%)
> 5*ULN	5/2497 (0.2%)	5/2376 (0.2%)
> 8*ULN	2/2497 (0.1%)	0/2376 (0%)
> 10*ULN	0/2497 (0%)	0/2376 (0%)
ALT or AST and Total bilirubin		
AT > 3*ULN and TBL > ULN	72/2473 (2.9%)	22/2334 (0.9%)
AT > 3xULN and TBL > 2xULN	14/2503 (0.6%)	1/2380 (<0.1%)
AT > 5xULN and TBL > ULN	57/2473 (2.3%)	15/2334 (0.6%)
AT > 5xULN and TBL > 2xULN	14/2503 (0.6%)	1/2380 (<0.1%)
AT > 8xULN and TBL > ULN	46/2473 (1.9%)	5/2334 (0.2%)
AT > 8xULN and TBL > 2xULN	11/2503 (0.4%)	1/2380 (<0.1%)
AT > 10xULN and TBL > ULN	35/2473 (1.4%)	4/2334 (0.2%)
AT > 10xULN and TBL > 2xULN	8/2503 (0.3%)	1/2380 (<0.1%)
AT > 20xULN and TBL > ULN	14/2473 (0.6%)	1/2334 (<0.1%)
AT > 20xULN and TBL > 2xULN	4/2503 (0.2%)	0/2380 (0%)
ALT or AST > 3*ULN and TBL > 2*ULN	14/2503 (0.6%)	1/2380 (<0.1%)
Biochemistry Hy's law:		
ALT or AST > 3*ULN and TBL > 2*ULN and ALP < 2*ULN	14/2489 (0.6%)	1/2370 (<0.1%)

Based on worst on-treatment values per Novartis Liver Toxicity guidelines
m: Number of subjects at risk for a specific category. For new abnormality post-baseline, this is the number of patients with both baseline and post-baseline evaluations, and baseline not meeting the criteria. For abnormal change from baseline, it is the number of patients with both baseline and post-baseline evaluations
N: Total number of subjects in the treatment group in this analysis set.
RD: Risk difference.
Patients with multiple events in a grouping are counted only once in the grouping.
MedDRA Version 26.0 and eCRS dated 26-Aug-2023 have been used for reporting.
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.
Source: Annex 7-Table 14.5-2.3a and iDFS Analysis Efficacy and Safety Update-Table 4-23

Table 8-5 Incidence of Hepatobiliary toxicity - HR-positive, HER2-negative advanced breast cancer(Safety Set)

	Pool		
AESI category	**RIBO + ET N=1065 n (%) (95% CI)**	**PBO + ET N=818 n (%) (95% CI)**	**RD RIBO + ET vs. PBO + ET (95% CI)**
ALL AEs	291 (27.3) (24.7, 30.1)	160 (19.6) (16.9, 22.4)	7.8 (3.9, 11.6)
CTC grade 3/4 AEs	141 (13.2) (11.3, 15.4)	50 (6.1) (4.6, 8.0)	7.1 (4.5, 9.7)
Related AEs	213 (20.0) (17.6, 22.5)	100 (12.2) (10.1, 14.7)	7.8 (4.5, 11.1)
AE requiring dose adjustment	36 (3.4) (2.4, 4.6)	10 (1.2) (0.6, 2.2)	2.2 (0.8, 3.5)
AE requiring dose interruption	121 (11.4) (9.5, 13.4)	36 (4.4) (3.1, 6.0)	7.0 (4.6, 9.3)
AEs leading to discontinuation	69 (6.5) (5.1, 8.1)	12 (1.5) (0.8, 2.5)	5.0 (3.3, 6.7)
SAEs	30 (2.8) (1.9, 4.0)	7 (0.9) (0.3, 1.8)	2.0 (0.8, 3.1)
On-treatment deaths	3 (0.3) (0.1, 0.8)	3 (0.4) (0.1, 1.1)	-0.1 (-0.6, 0.4)

Notable hepatic values (Safety Set)	**Pool**	
	RIBO + ET N=1065 n/m (%)	**PBO + ET N=818 n/m (%)**
AST		
>3xULN	152/1048 (14.5)	51/ 814 (6.3)
>5xULN	82/1048 (7.8)	16/ 814 (2.0)
>8xULN	48/1048 (4.6)	7/ 814 (0.9)
>10xULN	36/1048 (3.4)	3/ 814 (0.4)

>20xULN	12/1048 (1.1)	1/ 814 (0.1)
ALT		
>3xULN	177/1051 (16.8)	35/ 815 (4.3)
>5xULN	119/1051 (11.3)	13/ 815 (1.6)
>8xULN	71/1051 (6.8)	6/ 815 (0.7)
>10xULN	54/1051 (5.1)	3/ 815 (0.4)
>20xULN	21/1051 (2.0)	2/ 815 (0.2)
AST or ALT		
>3xULN	202/1051 (19.2)	60/ 815 (7.4)
>5xULN	129/1051 (12.3)	25/ 815 (3.1)
>8xULN	78/1051 (7.4)	12/ 815 (1.5)
>10xULN	59/1051 (5.6)	5/ 815 (0.6)
>20xULN	22/1051 (2.1)	2/ 815 (0.2)
Total bilirubin		
>ULN	61/1051 (5.8)	43/ 814 (5.3)
>2xULN	17/1051 (1.6)	10/ 814 (1.2)
ALP		
>1.5xULN	121/1051 (11.5)	106/ 815 (13.0)
>2xULN	80/1051 (7.6)	67/ 815 (8.2)
>3xULN	38/1051 (3.6)	30/ 815 (3.7)
>5xULN	14/1051 (1.3)	12/ 815 (1.5)
>8xULN	4/1051 (0.4)	6/ 815 (0.7)
>10xULN	0/1051	4/ 815 (0.5)
ALT or AST and Total bilirubin		
AT>3xULN & TBL>ULN	36/1050 (3.4)	16/ 814 (2.0)
AT>3xULN & TBL>2xULN	16/1050 (1.5)	9/ 814 (1.1)
AT>5xULN & TBL>ULN	32/1050 (3.0)	10/ 814 (1.2)
AT>5xULN & TBL>2xULN	15/1050 (1.4)	6/ 814 (0.7)
AT>8xULN & TBL>ULN	27/1050 (2.6)	8/ 814 (1.0)
AT>8xULN & TBL>2xULN	13/1050 (1.2)	5/ 814 (0.6)
AT>10xULN & TBL>ULN	25/1050 (2.4)	3/ 814 (0.4)
AT>10xULN & TBL>2xULN	11/1050 (1.0)	2/ 814 (0.2)
AT>20xULN & TBL>ULN	14/1050 (1.3)	1/ 814 (0.1)
AT>20xULN & TBL>2xULN	8/1050 (0.8)	0/ 814
Biochemistry Hy's law: ALT or AST>3xULN and total bilirubin>2xULN and ALP<2xULN	14/1050 (1.3)	6/ 814 (0.7)

Table 8-6 Hepatobiliary toxicity: Other details

Name of the risk	Hepatobiliary toxicity
Potential mechanisms	The most plausible mechanism underlying the liver effects of ribociclib is immune-mediated. Additionally, it could be due to multifactorial etiology (e.g. contributions from BSEP inhibition and reactive metabolite formation potentially leading to protein adduct formation)

Name of the risk	Hepatobiliary toxicity
Evidence source(s) and strength of evidence	Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. Preclinical data have reported fully reversible proliferative changes consistent with hepatobiliary toxicity. Specifically in dogs: the liver, the biliary system and the gallbladder showed proliferative changes, cholestasis, sand-like gallbladder calculi and thickening bile. These changes are not likely related to the primary pharmacology of ribociclib. The changes observed in the liver were mainly driven by the biliary duct system with, most likely, "bystander" effects on the surrounding hepatocytes and vasculature (i.e., locally irritating with additional cholestasis).
Characterization of the risk:	**CLEE011O12301C (NATALEE)- HR-positive, HER2-negative early breast cancer (Table 8-4)** • Hepatobiliary toxicity grouped AEs were reported more frequently in the ribociclib plus ET group (26.4% all grades; 8.6% ≥ grade 3) relative to the ET only group (11.2% all grades; 1.7% ≥ grade 3). The AEs suspected to be study drug related were reported in 21.9% in ribociclib plus ET group and 4.4% in ET only group. • Patients with hepatobiliary events in the ribociclib plus ET group were managed with either dose adjustment (2.6%) or interruption (12.4%). • Two hundred and twenty five patients (8.9%) in the ribociclib plus ET group and three patients (0.1%) in the ET only group discontinued the study treatment due to hepatobiliary events. • Twenty six patients (1.0 %) in the ribociclib plus ET group and five patients (0.2 %) in ET only group had hepatobiliary events considered SAE. • No on treatment deaths were reported in both the treatment groups. **Notable hepatic values:** Overall, the incidence of increased ALT or AST (>3×ULN) was greater in the ribociclib plus ET group compared to the ET only group (14.5% vs. 4.4%). Eighteen patients (0.7%) in the ribociclib plus ET group and 12 patients (0.5%) in the ET only group had total bilirubin increases greater than twice ULN. As of the data cut-off date, there were 15 treated patients whose LFT data met the biochemical criteria for Hy's Law (AST/ALT > 3 × ULN and TBL > 2 × ULN without ALP > 2 × ULN). Of these, 14 patients (0.6%) belonged to the ribociclib plus ET group and 1 patient (< 0.1%) to the ET only group. In addition to the 15 cases identified by the programmed algorithm, two cases meeting the Hy's Law criteria were identified manually based on the thorough medical evaluation of hepatobiliary toxicity events. Based on Novartis' comprehensive medical assessment, these 2 cases were considered to have met the biochemical criteria for Hy's Law, albeit (1) ALT/AST between TBL peaks had a longer lag-time; or (2) TBL equal to 2 × ULN; vs. the established criteria in both cases (FDA 2009). Of these 17 candidates considered to have met the criteria, 8 patients were clinically confirmed Hy's Law cases. All 8 patients were in the ribociclib plus ET treatment group. Among the 8 patients who developed notable hepatic values consistent with confirmed Hy's Law, the majority (n=6) completely recovered after discontinuation of ribociclib; 2 patients had improvement in lab values after ribociclib discontinuation, although still had mild lab

Name of the risk	Hepatobiliary toxicity
	abnormalities at the time of this analysis (1 patient with grade 2 elevated TBL; 1 patient with grade 1 elevated AST/ALT and grade 2 elevated TBL) as of DCO (21-Jul-2023). **HR-positive, HER2-negative advanced breast cancer- Pooled Data set: (Study E2301 – [NSAI], Study F2301, Study A2301)** • Hepatobiliary toxicity grouped AEs were reported more frequently in the ribociclib group (27.3% all grades; 13.2 grade 3/4) compared to the placebo group (19.6% all grades; 6.1% grade 3/4), with majority of the cases (20.0% vs.12.2%) being suspected to be related to study treatment. • Sixty nine patients (6.5%) in the ribociclib group and twelve patients (1.5%) discontinued due to hepatobiliary events. • Patients with hepatobiliary events were managed with either dose adjustment (3.4% vs 1.2%) or interruption (11.4% vs 4.4%). • Thirty patients (2.8 %) in the ribociclib group and seven patients (0.9%) had hepatobiliary events considered as a SAE. • Three on-treatment deaths were reported in the ribociclib group (0.3%). All these deaths occurred in settings of disease progression and were reported as not suspected to the study treatment (two deaths occurred more than one month after the last dose of ribociclib). • Exposure-adjusted incidence rates for hepatobiliary toxicity grouped AEs were 16.3 / 100 PTY in ribociclib group and 14.3 / 100 PTY in placebo group. **Notable hepatic values:** Biochemical Hy's Law was defined in a conservative way by taking into account non-concurrent values of ALT/AST/total bilirubin elevation and ALP depression throughout the treatment period. Fourteen patients (1.3%) in the ribociclib group, and six patients (0.7%) in the placebo group had hepatobiliary events which qualified for the Biochemical Hy's Law. As of the data cut-off, six out of these 14 patients in the ribociclib combination group were confirmed to meet Hy's law criteria (four from Study A2301 and two from Study F2301). Five of these six cases were suspected to be related to the study drug by the Investigator. All the patients were dosed at ribociclib 600 mg and grade 3 transaminase increases were detected within the first six months of treatment for all but one patient. Liver function test elevations in all patients recovered to baseline values following the discontinuation of ribociclib. None of the Hy's Law cases was fatal.
Risk factors and risk groups	There are no identified risk factors for the occurrence of hepatotoxicity (including liver laboratory abnormalities and Drug Induced Liver Injury [DILI]) in ribociclib-treated patients. Common causative/risk factors for hepatotoxicity include: • Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver, drug-drug interactions, and decreased drug clearance. • Alcohol abuse in patients with cirrhotic liver changes • Concomitant use of hepatotoxic medications.

Name of the risk	Hepatobiliary toxicity
Preventability	To minimize the risk of hepatobiliary toxicity, liver function must be closely monitored in all patients during treatment. Liver function tests should be performed before initiating therapy with ribociclib, then monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and subsequently as clinically indicated. Hepatobiliary toxicity can be managed in most of the cases by dose interruption and/or dose reduction (grade 2 and grade 3 increases in total bilirubin and/or transaminases); in some cases, like concomitant increase of transaminases and total bilirubin, or Grade 4 increases in transaminases and/or total bilirubin, treatment discontinuation is required. Current text in the SmPC (Section 4.2, Section 4.4, Section 4.8, and Section 5.3) addresses the risk in the patient population.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in patient with early breast cancer and advance or metastatic breast cancer.
Public health impact	The impact on public health is expected to be low. Liver enzyme elevations can be managed by appropriate monitoring of liver function tests, clinical symptoms and dose adjustments including interruption and permanent discontinuation.

8.3.1.3 Important identified risk: QT interval prolongation

Table 8-7 Incidence of QT interval prolongation- HR-positive, HER2-negative early breast cancer (Safety Set)

	CLEE011O12301C (NATALEE)		
AESI category	ET + Ribociclib N=2525 n(%) (95% CI)	ET Only N=2442 n(%) (95% CI)	RD ET + Ribociclib vs. ET Only (95% CI)
ALL AEs	134 (5.3) (4.5, 6.3)	34 (1.4) (1.0, 1.9)	3.9 (2.9, 4.9)
CTC grade >=3 AEs	26 (1.0) (0.7, 1.5)	15 (0.6) (0.3, 1.0)	0.4 (-0.1, 0.9)
AEs related to study treatment (Ribociclib and/or ET)	98 (3.9) (3.2, 4.7)	2 (0.1) (0.0, 0.3)	3.8 (3.0, 4.6)
AEs related to Ribociclib	98 (3.9) (3.2, 4.7)	0	3.9 (3.1, 4.6)
AEs related to ET	3 (0.1) (0.0, 0.3)	2 (0.1) (0.0, 0.3)	0.0 (-0.1, 0.2)
AE requiring dose adjustment	3 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.3)
AE requiring dose interruption	28 (1.1) (0.7, 1.6)	0	1.1 (0.7, 1.5)

AE requiring dose adjustment or interruption	29 (1.1) (0.8, 1.6)	0	1.1 (0.7, 1.6)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	10 (0.4) (0.2, 0.7)	0	0.4 (0.2, 0.6)
AEs leading to treatment discontinuation of Ribociclib	10 (0.4) (0.2, 0.7)	0	0.4 (0.2, 0.6)
AEs leading to treatment discontinuation of ET	0	0	
SAEs	5 (0.2) (0.1, 0.5)	2 (0.1) (0.0, 0.3)	0.1 (-0.1, 0.3)
On-treatment deaths	1 (<0.1) (0.0, 0.2)	0	0.0 (0.0, 0.1)

Notable ECG values (Safety set)

QTcF interval	**Ribociclib + ET N=2525 n/m (%)**	**ET only N=2442 n/m (%)**	**Total N=4967 n/m (%)**
New value > 450	240/2477 (9.7%)	67/2365 (2.8%)	307/4842 (6.3%)
New value > 480	10/2493 (0.4%)	4/2378 (0.2%)	14/4871 (0.3%)
New value > 500	3/2493 (0.1%)	1/2378 (<0.1%)	4/4871 (0.1%)
Increase from baseline of > 30	466/2493 (18.7%)	167/2378 (7.0%)	633/4871 (13.0%)
Increase from baseline of > 60	19/2493 (0.8%)	2/2378 (0.1%)	21/4871 (0.4%)
QT interval			
New > 450	222/2460 (9.0%)	105/2349 (4.5%)	327/4809 (6.8%)
New > 480	39/2492 (1.6%)	15/2377 (0.6%)	54/4869 (1.1%)
New > 500	7/2493 (0.3%)	1/2377 (<0.1%)	8/4870 (0.2%)
Increase from baseline of > 30	1049/2493 (42.1%)	591/2378 (24.9%)	1640/4871 (33.7%)
Increase from baseline of > 60	170/2493 (6.8%)	47/2378 (2.0%)	217/4871 (4.5%)

Patients are counted based on any notable ECG post-baseline value
ECG assessments based on central laboratory results only
Baseline is defined as the last assessment on or before start of study treatment. For any replicate/triplicate ECGs per time point, the average of these measurements would be calculated for baseline
n: Number of subjects who meet the designated criterion
m: Number of subjects at risk for a specific category. For new abnormality post-baseline, this is the number of patients with both baseline and post-baseline evaluations, and baseline not meeting the criteria. For abnormal change from baseline, it is the number of patients with both baseline and post-baseline evaluations
N: Total number of subjects in the treatment group in this analysis set
RD: Risk difference
Patients with multiple events in a grouping are counted only once in the grouping
MedDRA Version 26.0 and eCRS dated 26-Aug-2023 have been used for reporting.
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.
Source: Annex 7-Table 14.5-2.3g, Annex 7-Table 14.3-5.3a and iDFS Analysis Efficacy and Safety Update-Table 4-26.

Table 8-8 Incidence of QT interval prolongation- HR-positive, HER2-negative advanced breast cancer(Safety Set)

AESI category	Pool		
	RIBO + ET N=1065 n (%) (95% CI)	**PBO + ET N=818 n (%) (95% CI)**	**RD RIBO + ET vs. PBO + ET (95% CI)**
ALL AEs	99 (9.3) (7.6, 11.2)	29 (3.5) (2.4, 5.1)	5.8 (3.6, 7.9)
CTC grade 3/4 AEs	34 (3.2) (2.2, 4.4)	11 (1.3) (0.7, 2.4)	1.8 (0.5, 3.2)
Related AEs	69 (6.5) (5.1, 8.1)	9 (1.1) (0.5, 2.1)	5.4 (3.7, 7.0)
AE requiring dose adjustment	15 (1.4) (0.8, 2.3)	2 (0.2) (0.0, 0.9)	1.2 (0.4, 1.9)
AE requiring dose interruption	20 (1.9) (1.2, 2.9)	3 (0.4) (0.1, 1.1)	1.5 (0.6, 2.4)
AEs leading to discontinuation	5 (0.5) (0.2, 1.1)	3 (0.4) (0.1, 1.1)	0.1 (-0.5, 0.7)
SAEs	13 (1.2) (0.7, 2.1)	3 (0.4) (0.1, 1.1)	0.9 (0.1, 1.6)
On-treatment deaths	3 (0.3) (0.1, 0.8)	0	0.3 (0.0, 0.6)
Notable ECG values (Safety Set)			
	Pool		
	RIBO + ET	**PBO + ET**	

	N=1065 n/m (%)	N=818 n/m (%)
QTcF (ms)		
New > 450	417/1037(40.2)	124/ 793(15.6)
New > 480	55/1054 (5.2)	12/ 814 (1.5)
New > 500	15/1054 (1.4)	3/ 814 (0.4)
Increase from baseline > 30	510/1054 (48.4)	124/ 815 (15.2)
Increase from baseline > 60	61/1054 (5.8)	3/ 815 (0.4)
QT (ms)		
New > 450	235/1039 (22.6)	71/ 798 (8.9)
New > 480	75/1054 (7.1)	8/ 815 (1.0)
New > 500	18/1054 (1.7)	1/ 815 (0.1)
Increase from baseline > 30	696/1054 (66.0)	315/ 815 (38.7)
Increase from baseline > 60	232/1054 (22.0)	30/ 815 (3.7)
HR (bpm)		
Increase from baseline > 25% & to a value > 100	56/1054 (5.3)	42/ 814 (5.2)
Decrease from baseline >25% & to a value < 50	20/1054 (1.9)	4/ 814 (0.5)
PR (ms)		
New >200	74/1009 (7.3)	42/ 784 (5.4)
Increase from baseline >25% & to a value >200	24/1051 (2.3)	4/ 811 (0.5)
QRS (ms)		
New >110	20/1040 (1.9)	17/ 802 (2.1)
Increase from baseline >25% & to a value >110	12/1054 (1.1)	6/ 815 (0.7)

Table 8-9 QT interval prolongation: Other details

Name of the risk	QT interval prolongation
Potential mechanisms	Nonclinical studies suggest that ribociclib has the potential to delay ventricular repolarization in humans. Based on *in vitro* electrophysiology data and achieved free Cmax at the 600 mg dose, ribociclib is considered to contribute to the majority of the QTc interval prolongation in human, with minimal contribution of LEQ803 (metabolite of ribociclib accounting for <10% of parent exposure in humans).
Evidence source(s) and strength of evidence	In vivo cardiac safety studies in dogs demonstrated a dose and concentration related QTcF interval prolongation at an exposure achieved in patients following the recommended dose of 600 mg with the potential to induce incidences of premature ventricular contractions at higher exposure levels (approximately 5-fold the anticipated clinical Cmax). There were no effects on heart rate, blood pressure, core body temperature, or other ECG findings.
Characterization of the risk:	Serial, triplicate ECGs were collected following a single dose and at steady state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1200 mg. The analysis suggested that ribociclib causes concentration dependent increases in the QTc interval. The estimated QTcF mean change from baseline for 600 mg Kisqali in combination with NSAI or fulvestrant was 22.0 msec (90% CI: 20.56, 23.44) and 23.7 msec (90% CI: 22.31, 25.08), respectively at the geometric mean Cmax at steady state compared to 34.7 msec (90% CI: 31.64, 37.78) in combination with tamoxifen. Kisqali is not recommended to be used in combination with tamoxifen. At the geometric mean steady-state Cmax of the ribociclib 400 mg dose with NSAI (letrozole or anastrozole) as combination partner evaluated in patients with early breast cancer in Study O12301C, the model-estimated geometric mean ΔQTcF was 10.0 ms (90% CI: 8.02, 11.91). **CLEE011O12301C (NATALEE)- HR-positive, HER2-negative early breast cancer (Table 8-7)** • QT interval prolongation events were reported slightly more frequently in the ribociclib plus ET group (5.3% all grades; 1.0% grade ≥3) relative to the ET group (1.4% all grades; 0.6% grade ≥3). The AEs suspected to be study drug related were reported in 3.9% in ribociclib plus ET group and 0.1% in ET only group. • Patients with QT interval prolongation events in the ribociclib plus ET group were managed with either dose adjustment (0.1%) or interruption (1.1%). • Ten patients (0.4%) in the ribociclib plus ET group and none in ET only group discontinued the study treatment due to QTc interval prolongation. • Five patients (0.2%) in the ribociclib plus ET and two patient (0.1%) in ET only group had QT interval prolongation events considered SAE. • One on-treatment death due to a cardiac arrest was reported in ribociclib plus ET group. The patient has been off ribociclib approximately for 6 weeks prior to the event due to a physician decision while continuing ET therapy in the context of study treatment. The event was not associated with electrocardiogram

Name of the risk	QT interval prolongation
	QT prolonged and was assessed as not suspected to ribociclib or ET by the Investigator (iDFS analysis safety and efficacy update). **Notable ECG value:** The incidence of notable ECG values based on central review was infrequent and numerically comparable between the two treatment groups. In the ribociclib plus ET group, new QTcF > 480 ms or > 500 ms was observed in 10 patients (0.4%) and 3 patients (0.1%), respectively; while in the ET only group, new QTcF >480 ms or > 500 ms was observed in 4 patients (0.2%) and 1 patient (< 0.1%), respectively. An increase > 60 ms from baseline in QTcF interval was observed in 19 patients (0.8%) in the ribociclib plus ET group and in 2 patients (0.1%) in the ET only group. Among 19 patients in the ribociclib plus ET group who developed increase in QTcF interval > 60 ms from baseline, the majority (14 out of 19) did not result in clinically meaningful ECG abnormalities: the QTcF remained < 450 ms in 5 patients and QTcF remained between 450-480ms (QTcF interval prolonged grade 1 by CTCAE) in 9 patients, not requiring any action with ribociclib; in the remaining 5 out 19 patients who developed increased in QTcF > 60 ms from baseline, 2 resulted in QTcF > 480ms and < 500ms and 3 resulted in QTcF > 500 ms, of which were included in the discussion above (iDFS analysis efficacy and safety update). **HR-positive, HER2-negative advanced breast cancer - Pooled Data set: (Study E2301 – [NSAI], Study F2301, Study A2301)** • QTc interval prolongation events were reported more frequently in the ribociclib group (9.3% all grades; 3.2% grade 3/4) compared to the placebo group (3.5% all grades; 1.3% grade 3/4), with majority of the cases (6.5% vs.1.1%) being suspected to be related to study treatment. • Five patients (0.5%) in the ribociclib group and three patients (0.4%) in placebo group discontinued due to QTc interval prolongation. Patients with QTc interval prolongation events were managed with either dose adjustment (1.4% vs 0.2%) or interruption (1.9% vs 0.4%). • Thirteen patients (1.2%) in the ribociclib group and three patients (0.4%) in placebo group had QTc interval prolongation events considered as a SAE. • Three on-treatment deaths were reported in the ribociclib group (0.3%), two of them were reported as not suspected to the study treatment (one occurred 27 days after the last dose of ribociclib and the other one 2 days after the last dose of ribociclib due to complications from severe head traumatism), and the third case was suspected to be related to ribociclib for which no conclusion could be drawn with regards to the QTc evolution during the trial and with several confounders such as Grade 3 hypokalemia and Grade 2 QT prolongation. • Exposure-adjusted incidence rates for QT interval prolongation grouped AEs were 4.8 / 100 PTY in ribociclib group and 2.3 / 100 PTY in placebo group. Notable ECG values in patients included in the Safety set • Higher QTcF values (40.2% vs 15.6%) were observed in patients in the ribociclib group compared with placebo group. QTcF values

Name of the risk	QT interval prolongation
	of >500 ms were observed in 15 patients (1.4%) in the ribociclib group and in three patients (0.4%) in the placebo group. • A >60 ms increase from Baseline in QTcF interval was observed in 62 patients (5.8%) in the ribociclib group and in two patients (0.4%) in the placebo group.
Risk factors and risk groups	Patients with history of cardiac disease, electrolyte imbalances (hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia), and concomitant intake of QT-prolonging drugs. The co-administration of medications that may increase the risk of QTc prolongation such as strong CYP3A4 inhibitors; and medications that have a known risk for QT prolongation.
Preventability	ECG should be assessed before initiating treatment with Kisqali in all patients. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. For early breast cancer, ECG should be repeated at approximately day 14 of the first cycle, then as clinically indicated. For advanced or metastatic breast cancer, ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended in patients with early breast cancer and advanced or metastatic breast cancer. Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali. Use of Kisqali with medicinal products known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval. In patients with advanced or metastatic breast cancer, if a strong CYP3A4 inhibitor must be co-administered, the dose of Kisqali should be reduced to 400 mg once daily. Patients with advanced or metastatic breast cancer who have had their dose reduced to 400 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, should be monitored for adverse reactions. If necessary, a reduction of the Kisqali dose to 200 mg should be considered. Patients with advanced or metastatic breast cancer who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, should be monitored for adverse reactions. If necessary, treatment with Kisqali should be interrupted. In patients with early breast cancer, If a strong CYP3A4 inhibitor must be co-administered, patients should be monitored for adverse reactions and, if necessary, a reduction of Kisqali dose to 200 mg should be considered. Patients with early breast cancer who have had their dose reduced to 200 mg ribociclib daily, and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, should be monitored for adverse reactions. If necessary, treatment with Kisqali should be interrupted. (SmPC). ECG and serum electrolytes monitoring should be done prior to and during treatment with ribociclib, and as clinically indicated. Dosage modification

Name of the risk	QT interval prolongation
	and management guidelines are recommended for QT prolongation in the prescribing information. Current text in the SmPC (Section 4.2, Section 4.4, Section 4.5, Section 4.8, Section 5.1 and Section 5.3) addresses the risk in the patient population.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in patient with early breast cancer and advanced or metastatic breast cancer.
Public health impact	With regular monitoring, prompt dose modification and treatment where indicated, the public health concern is low.

8.3.1.4 Important identified risk: Reproductive Toxicity

Table 8-10 Incidence of Reproductive toxicity- HR-positive, HER2-negative early breast cancer (Safety Set)

	CLEE011O12301C (NATALEE)		
AESI category	ET + Ribociclib N=2525 n(%) (95% CI)	ET Only N=2442 n(%) (95% CI)	RD ET + Ribociclib vs. ET Only (95% CI)
ALL AEs	32 (1.3) (0.9, 1.8)	27 (1.1) (0.7, 1.6)	0.2 (-0.4, 0.8)
CTC grade >=3 AEs	8 (0.3) (0.1, 0.6)	7 (0.3) (0.1, 0.6)	0.0 (-0.3, 0.3)
AEs related to study treatment (Ribociclib and/or ET)	5 (0.2) (0.1, 0.5)	1 (<0.1) (0.0, 0.2)	0.2 (0.0, 0.3)
AEs related to Ribociclib	4 (0.2) (0.0, 0.4)	0	0.2 (0.0, 0.3)
AEs related to ET	1 (<0.1) (0.0, 0.2)	1 (<0.1) (0.0, 0.2)	0.0 (-0.1, 0.1)
AE requiring dose adjustment	0	0	
AE requiring dose interruption	12 (0.5) (0.2, 0.8)	1 (<0.1) (0.0, 0.2)	0.4 (0.2, 0.7)
AE requiring dose adjustment or interruption	12 (0.5) (0.2, 0.8)	1 (<0.1) (0.0, 0.2)	0.4 (0.2, 0.7)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	2 (0.1) (0.0, 0.3)	1 (<0.1) (0.0, 0.2)	0.0 (-0.1, 0.2)
AEs leading to treatment discontinuation of Ribociclib	2 (0.1) (0.0, 0.3)	0	0.1 (0.0, 0.2)
AEs leading to treatment discontinuation of ET	0	1 (<0.1) (0.0, 0.2)	0.0 (-0.1, 0.0)
SAEs	5 (0.2) (0.1, 0.5)	5 (0.2) (0.1, 0.5)	0.0 (-0.3, 0.2)
On-treatment deaths	0	0	

	CLEE011O12301C (NATALEE)		
AESI category	**ET + Ribociclib N=2525 n(%) (95% CI)**	**ET Only N=2442 n(%) (95% CI)**	**RD ET + Ribociclib vs. ET Only (95% CI)**

RD: Risk difference
Patients with multiple events in a grouping are counted only once in the grouping
MedDRA Version 26.0 and eCRS dated 26-Aug-2023 have been used for reporting.
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.
Source: Annex 7-Table 14.5-2.3i

Table 8-11 Incidence of Reproductive toxicity- HR-positive, HER2-negative advanced breast cancer(Safety Set)

AESI category	Pool		RD RIBO + ET vs. PBO + ET (95% CI)
	RIBO + ET N=1065 n (%) (95% CI)	PBO + ET N=818 n (%) (95% CI)	
ALL AEs	6 (0.6) (0.2, 1.2)	6 (0.7) (0.3, 1.6)	-0.2 (-0.9, 0.6)
CTC grade 3/4 AEs	1 (0.1) (0.0, 0.5)	0	0.1 (-0.1, 0.3)
Related AEs	1 (0.1) (0.0, 0.5)	0	0.1 (-0.1, 0.3)
AE requiring dose adjustment	0	0	-
AE requiring dose interruption	1 (0.1) (0.0, 0.5)	0	0.1 (-0.1, 0.3)
AEs leading to discontinuation	0	0	-
SAEs	0	0	-
On-treatment deaths	0	0	-

RD: Risk difference.
Patients with multiple events in a grouping are counted only once in the grouping.
MedDRA Version 24.0 and eCRS dated 16-Jun-2021 have been used for reporting.
Source: Annex-7 Table 4-2.14k

Table 8-12 Reproductive Toxicity: Other details

Name of the risk	Reproductive Toxicity
Potential mechanisms	A study reported in the literature suggests that inhibition of CDK4/6 during late stages of fetal development may be significantly toxic by causing severe anemia. Mouse fetuses that did not express CDK4/6 died starting on embryonic Day 14.5 with an increased frequency until birth, shortly after which no CDK4/6 deficient pups remained alive (Malumbres et al 2004). However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.
Evidence source(s) and strength of evidence	Based on findings in animals and mechanism of action, ribociclib could cause fetal harm when administered to a pregnant woman. Ribociclib caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below and 1.5 times the human clinical exposure based on area under the curve (AUC). Based on animal studies, ribociclib could impair fertility in males of reproductive potential (Non clinical overview, SmPC). Although, there is no available human data confirming the drug-associated risk, considering the potential impact of this risk in the clinical setting based on clear non-clinical findings, this is categorized as an important identified risk.
Characterization of the risk:	**CLEE011O12301C (NATALEE)- HR-positive, HER2-negative early breast cancer (Table 8-10)** • Reproductive Toxicity grouped AEs were almost similar in the ribociclib plus ET group (1.3% all grades; 0.3% ≥ grade 3) relative to the ET only group (1.1% all grades; 0.3% ≥ grade 3). • The most frequently reported AE in both treatment groups was mastitis (all grades: 1.1% in the ribociclib plus ET group and 0.8% in the ET only group; ≥ grade 3: 0.3% in the ribociclib plus ET group and 0.2% in the ET only group). The event mastitis is retrieved due to the broadness of the reproductive toxicity AESI search criteria CLEE011O12301C CSR-Section 12.3.2.7 and iDFS analysis efficacy and safety. • Two patients (0.1%) in the ribociclib plus ET group discontinued the study treatment due to mastitis and one patient (<0.1%) in ET only group discontinued the study treatment due to BRCA1 gene mutation and BRCA2 gene mutation. • Overall, incidence of SAEs (0.2%) was similar between the treatment arms and none of the SAE was indicative of reproductive toxicity. Five patients in the ribociclib plus ET group reported AEs that were considered serious (4 patients (0.2%): mastitis and 1 patient (< 0.1%): polycystic liver disease). Five patients (0.2%) in the ET only group reported at least 1 reproductive toxicity SAE (2 patients, 0.1%: mastitis and 3 patients: one event each of BRCA1 gene mutation, BRCA2 gene mutation, and renal arteriovenous malformation). • There were 2 pregnancies reported in the study, however none was reported while the patients were exposed to ribociclib. One patient had a positive test at screening and was discontinued from the study prior to starting treatment. Another patient reported pregnancy more than 30 days after the last dose of ribociclib, letrozole and goserelin (CLEE011O12301C CSR). • No on treatment deaths was reported in both the treatment groups.

Name of the risk	Reproductive Toxicity
	HR-positive, HER2-negative advanced breast cancer - Pooled Data set: (Study E2301 – [NSAI], Study F2301, Study A2301): • Reproductive Toxicity grouped AEs were almost similar in the ribociclib group (0.6 % all grades; 0.1% grade 3/4) compared to the placebo group (0.7% all grades). • The retrieved events included: mastitis, omphalitis, arteriovenous malformation, chloasma and cystic fibrosis, these events were retrieved in the search due to the conservative use of a broad Standardized MedDRA Query (SMQ). • No pregnancies have been reported in patients treated with ribociclib. • None of the patients discontinued due to AEs, nor was any dose adjustment or interruption needed. • No SAEs and on-treatment deaths were reported in both the treatment groups. • Exposure-adjusted incidence rates for reproductive toxicity grouped AEs were 0.3 / 100 PTY in ribociclib group and 0.5 / 100 PTY in placebo group.
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with ribociclib through pregnancy are at a risk.
Preventability	Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with ribociclib and should use effective contraception (methods that result in less than 1% pregnancy rates) during ribociclib treatment and for at least 21 days after last dose of ribociclib. If ribociclib is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the risk to a fetus (SmPC). Current text in the SmPC (Section 4.4, Section 4.6 and Section 5.3) addresses the risk in the patient population.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a low impact on the benefit-risk balance in patient with early breast cancer and advanced or metastatic breast cancer, considering the effective contraceptive recommendations provided in the prescribing information.
Public health impact	The public health impact is low considering the effective contraceptive recommendations provided in the prescribing information.

8.3.1.5 Important Potential risk: Renal toxicity

Table 8-13 Incidence of Renal toxicity- HR-positive, HER2-negative early breast cancer (Safety Set)

AESI category	ET + Ribociclib N=2525 n(%) (95% CI)	ET Only N=2442 n(%) (95% CI)	RD ET + Ribociclib vs. ET Only (95% CI)
ALL AEs	152 (6.0) (5.1, 7.0)	58 (2.4) (1.8, 3.1)	3.6 (2.5, 4.8)
CTC grade >=3 AEs	7 (0.3) (0.1, 0.6)	0	0.3 (0.1, 0.5)
AEs related to study treatment (Ribociclib and/or ET)	97 (3.8) (3.1, 4.7)	26 (1.1) (0.7, 1.6)	2.8 (1.9, 3.6)
AEs related to Ribociclib	93 (3.7) (3.0, 4.5)	0	3.7 (2.9, 4.4)
AEs related to ET	17 (0.7) (0.4, 1.1)	26 (1.1) (0.7, 1.6)	-0.4 (-0.9, 0.1)
AE requiring dose adjustment	4 (0.2) (0.0, 0.4)	0	0.2 (0.0, 0.3)
AE requiring dose interruption	22 (0.9) (0.5, 1.3)	0	0.9 (0.5, 1.2)
AE requiring dose adjustment or interruption	22 (0.9) (0.5, 1.3)	0	0.9 (0.5, 1.2)
AEs leading to study treatment discontinuation (Ribociclib and/or ET)	9 (0.4) (0.2, 0.7)	0	0.4 (0.1, 0.6)
AEs leading to treatment discontinuation of Ribociclib	9 (0.4) (0.2, 0.7)	0	0.4 (0.1, 0.6)
AEs leading to treatment discontinuation of ET	1 (<0.1) (0.0, 0.2)	0	0.0 (0.0, 0.1)
SAEs	2 (0.1) (0.0, 0.3)	1 (<0.1) (0.0, 0.2)	0.0 (-0.1, 0.2)
On-treatment deaths	0	0	

RD: Risk difference
Patients with multiple events in a grouping are counted only once in the grouping
MedDRA Version 26.0 and eCRS dated 26-Aug-2023 have been used for reporting.
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.
Source: Annex 7-Table 14.5-2.3h

Table 8-14 Incidence of Renal toxicity- HR-positive, HER2-negative advanced breast cancer (Safety Set)

AESI category	Pool	

	RIBO + ET N=1065 n (%) (95% CI)	PBO + ET N=818 n (%) (95% CI)	RD RIBO + ET vs. PBO + ET (95% CI)
ALL AEs	122 (11.5) (9.6, 13.5)	34 (4.2) (2.9, 5.8)	7.3 (4.9, 9.7)
CTC grade 3/4 AEs	14 (1.3) (0.7, 2.2)	7 (0.9) (0.3, 1.8)	0.5 (-0.5, 1.4)
Related AEs	52 (4.9) (3.7, 6.4)	10 (1.2) (0.6, 2.2)	3.7 (2.2, 5.2)
AE requiring dose adjustment	7 (0.7) (0.3, 1.3)	2 (0.2) (0.0, 0.9)	0.4 (-0.2, 1.0)
AE requiring dose interruption	24 (2.3) (1.4, 3.3)	8 (1.0) (0.4, 1.9)	1.3 (0.2, 2.4)
AEs leading to discontinuation	7 (0.7) (0.3, 1.3)	1 (0.1) (0.0, 0.7)	0.5 (0.0, 1.1)
SAEs	16 (1.5) (0.9, 2.4)	5 (0.6) (0.2, 1.4)	0.9 (0.0, 1.8)
On-treatment deaths	0	0	-

RD: Risk difference.
Patients with multiple events in a grouping are counted only once in the grouping.
MedDRA Version 24.0 and eCRS dated 16-Jun-2021 have been used for reporting.
Source: Annex-7 Table 4-2.14j

Table 8-15 Renal toxicity: Other details

Name of the risk	Renal toxicity
Potential mechanisms	Mechanism of blood creatinine elevations is related to ribociclib-induced inhibition of the renal transporters organic cation transporter2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1), which are involved in the active secretion of creatinine from the proximal tubules.
Evidence source(s) and strength of evidence	Reversible degeneration of the kidney tubular epithelial cells has been observed in the 15- and 27-week rat toxicity studies. Cases of creatinine increased have been reported in clinical studies. The endogenous marker, cystatin C, was measured to further investigate renal function, and no obvious changes in cystatin C levels were observed following a single 400 mg dose of ribociclib, suggesting ribociclib does not cause direct renal toxicity (Study A2116 Interim report Part 1 dated 02-Feb-2018).
Characterization of the risk:	**CLEE011O12301C (NATALEE)- HR-positive, HER2-negative early breast cancer (Table 8-13)** • Slightly higher incidences of renal toxicity grouped AEs, including grade 3 and 4 events, were observed in the ribociclib plus ET group (6.0% all grades, and 0.3% ≥ grade 3) relative to the ET group (2.4% all grades, and no AEs ≥ grade 3). The AEs suspected to be study drug related were reported in 3.8% in ribociclib plus ET group and 1.1% in ET only group.

Name of the risk	Renal toxicity
	• The most common renal toxicity event was blood creatinine increased (all grades: 3.9% in ribociclib plus ET group; 0.9% in ET only group) (iDFS analysis efficacy and safety update). • Patients with renal toxicity events in the ribociclib plus ET group were managed with either dose adjustment (0.2%) or interruption (0.9%). • Nine patients (0.4%) in the ribociclib plus ET group and none in ET only discontinued the study treatment due to renal toxicity events. • Two patients (0.1%) in the ribociclib plus ET group and one patient (<0.1%) in ET only group had renal toxicity events considered SAE. • No on-treatment deaths were reported in both the treatment groups. **HR-positive, HER2-negative advanced breast cancer - Pooled Data set: (Study E2301 – [NSAI], Study F2301, Study A2301)**: • Higher incidences of renal toxicity grouped AEs, including grade 3 and 4 events, were observed in the ribociclib group (11.5% all grades, and 1.3% grade 3/4) relative to the placebo group (4.2% all grades, and 0.9% grade 3/4). Most of these events were suspected to be study drug related (4.9% vs 1.2%). • The majority of the events were blood creatinine increased (7.9% in the ribociclib group vs 2.4% in the placebo group), and of mild grade, and were reversible. • Seven patients (0.7%) in the ribociclib group and one patient (0.1%) in the placebo group discontinued due to renal toxicity events. • Patients with renal toxicity events in the ribociclib group were managed with either dose adjustment (0.7%) or interruption (2.3%). • Sixteen patients (1.5%) in the ribociclib group and five patients (0.6%) in the placebo group had renal toxicity events considered as a serious adverse event (SAE). • No on treatment deaths were reported in both the treatment groups. • Exposure-adjusted incidence rates for renal toxicity grouped AEs were 6.0 / 100 PTY in ribociclib group and 2.7 / 100 PTY in placebo group.
Risk factors and risk groups	Patients with severe renal dysfunction Patients with severe dehydration.
Preventability	Current text in the SmPC (Section 4.2, Section 4.8 and Section 5.2) addresses the risk in the patient population.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in patient with early breast cancer and advanced or metastatic breast cancer.
Public health impact	Considering the magnitude and severity of these renal events in the clinical setting, the public health concern is deemed low.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-16 Missing information: Safety in Japanese patients

Name of missing information	Safety in Japanese patients
Evidence source	A majority of patients in the main clinical studies were Caucasians. Results from two clinical studies which evaluated KISQALI exposure as a single agent in Japanese patients with advanced cancers, showed increases in drug concentration in the blood as dose increased. However, this data is too limited to make definitive conclusions in this population.
Anticipated risk/ consequence of the missing information:	A higher exposure with ribociclib as compared to non-Japanese patients with the same dose may potentially lead to more dose limiting toxicities.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	Myelosuppression Hepatobiliary toxicity QT interval prolongation Reproductive toxicity
Important potential risks	Renal toxicity
Missing information	Safety in Japanese patients

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific targeted follow-up questionnaires for risks:

Specific targeted follow-up questionnaires will be used to collect further data to help characterize and/or closely monitor each of the respective risks

The following targeted follow-up questionnaires are used to collect additional data for ribociclib:

Liver or hepatobiliary AEs/Liver Injury

QT Interval prolongation or Torsades de Pointes

These targeted follow up questionnaires are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities for risks

Not applicable.

10.2 Part III.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities.

11 Part IV: Plans for post-authorization efficacy studies

Table 11-1 Ongoing post-authorization efficacy studies that are conditions of the marketing authorization

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
NATALEE (CLEE011O12301C) (Ongoing)	The purpose of this trial is to evaluate the effect of the addition of ribociclib to standard adjuvant ET on iDFS in patients with HR-positive, HER2-negative Anatomic Stage Group III, IIB or a subset of Stage IIA eBC	To further evaluate the efficacy and safety of ribociclib for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer, in combination with an aromatase inhibitor	5-year follow-up of iDFS and OS in the NATALEE study report.	30-Jun-2027

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

12.1 Part V.1. Routine risk minimization measures

Description of routine risk minimization measures by safety concern

Table 12-1 Risk minimization measures for Myelosuppression

Safety concern	Myelosuppression
	Routine risk communication Addressed in Section 4.2, Section 4.4 and Section 4.8 of the SmPC and Section 2 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Safety monitoring and dose modification guidance as recommended in sections 4.2 and 4.4 of the SmPC. Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication. **Other routine risk minimization measures beyond the Product Information** None

Table 12-2 Risk minimization measures for Hepatobiliary toxicity

Safety concern	Hepatobiliary toxicity
	Routine risk communication Addressed in Section 4.2, Section 4.4, Section 4.8, and Section 5.3 of the SmPC and Section 2 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Safety monitoring and dose modification guidance as recommended in sections 4.2 and 4.4 of the SmPC. Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication. **Other routine risk minimization measures beyond the Product Information** None

Table 12-3 Risk minimization measures for QT interval prolongation

Safety concern	QT interval prolongation
	Routine risk communication Addressed in Section 4.2, Section 4.4, Section 4.5, Section 4.8, Section 5.1 and Section 5.3 of the SmPC and Section 2 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Safety monitoring and dose modification guidance as recommended in sections 4.2 and 4.4 of the SmPC. Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication. **Other routine risk minimization measures beyond the Product Information** None

Table 12-4 Risk minimization measures for Reproductive Toxicity

Safety concern	Reproductive Toxicity
	Routine risk communication Addressed in Section 4.4, Section 4.6 and Section 5.3 of the SmPC and Section 2 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Pregnancy status should be verified prior to starting treatment with Kisqali. Women of reproductive potential should be advised to use effective contraception during treatment with Kisqali and for at least 21 days after the last dose. **Other routine risk minimization measures beyond the Product Information** None

Table 12-5 Risk minimization measures for Renal toxicity

Safety concern	Renal toxicity
	Routine risk communication Addressed in Section 4.2, Section 4.8 and Section 5.2 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication. **Other routine risk minimization measures beyond the Product Information** None

Table 12-6 Risk minimization measures for by Safety in Japanese patients

Safety concern	Safety in Japanese patients
	Routine risk communication Currently available data are limited and do not support the need for risk minimization. **Routine risk minimization activities recommending specific clinical measures to address the risk:** none Prescription only medicine, treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies and to be used in the approved indication. **Other routine risk minimization measures beyond the Product Information** None

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-7 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Myelosuppression	Section 4.2, Section 4.4 and Section 4.8 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hepatobiliary toxicity	Section 4.2, Section 4.4, Section 4.8, and Section 5.3 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
QT interval prolongation	Section 4.2, Section 4.4, Section 4.5, Section 4.8, Section 5.1 and Section 5.3 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Reproductive Toxicity	Section 4.4, Section 4.6 and Section 5.3 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Renal toxicity	Section 4.2, Section 4.8 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in Japanese patients	Currently available data are limited and do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

13 Part VI: Summary of the risk management plan for KISQALI® (ribociclib)

This is a summary of the risk management plan (RMP) for KISQALI®. The RMP details important risks of KISQALI®, how these risks can be minimized, and how more information will be obtained about KISQALI® risks and uncertainties (missing information).

KISQALI® summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KISQALI® should be used.

This summary of the RMP for KISQALI® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates to the KISQALI® RMP.

13.1 Part VI: I. The medicine and what it is used for

KISQALI® is authorised for:

- Treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.
- Adjuvant treatment of patients with HR-positive, HER2-negative stage II and III early breast cancer, irrespective of nodal status, in combination with an aromatase inhibitor. In pre- or perimenopausal women, or men, the aromatase inhibitor should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Additional details on the both the indications are available in the SmPC.

Route of administration, pharmaceutical forms and strengths:

KISQALI® is available as 200 mg film-coated tablets for oral administration. Additional details on the approved information on route of administration are available in the SmPC.

Further information about the evaluation of KISQALI® benefits can be found in KISQALI® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004213/WC500234000.pdf (last accessed: 21-09-2018).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of KISQALI® together with measures to minimize such risks and the proposed studies for learning more about KISQALI®'s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of KISQALI®, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of KISQALI® is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of KISQALI® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of KISQALI®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Myelosuppression Hepatobiliary toxicity QT interval prolongation Reproductive Toxicity
Important potential risks	Renal toxicity
Missing information	Safety in Japanese patients

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk - Myelosuppression

Evidence for linking the risk to the medicine	Bone marrow hypocellularity was predicted by preclinical studies and is considered to be related to the pharmacological inhibition of cell replication due to CDK4/6 inhibition. Neutropenia has been the most

	common toxicity observed in clinical practice. Grade 3 or 4 neutropenia including febrile neutropenia has been reported as dose-limiting toxicities in single-agent ribociclib trials.
Risk factors and risk groups	Patients with low baseline neutrophil and/or leukocyte counts.
Risk minimization measures	**Routine risk minimization measures:** Addressed in Section 4.2, Section 4.4 and Section 4.8 of the SmPC and Section 2 of PL. **Additional risk minimization measures**: None

Table 13-3 Important identified risk - Hepatobiliary toxicity

Evidence for linking the risk to the medicine	Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. Preclinical data have reported fully reversible proliferative changes consistent with hepatobiliary toxicity. Specifically in dogs: the liver, the biliary system and the gallbladder showed proliferative changes, cholestasis, sand-like gallbladder calculi and thickening bile. These changes are not likely related to the primary pharmacology of ribociclib. The changes observed in the liver were mainly driven by the biliary duct system with, most likely, "bystander" effects on the surrounding hepatocytes and vasculature (i.e., locally irritating with additional cholestasis).
Risk factors and risk groups	There are no identified risk factors for the occurrence of hepatotoxicity (including liver laboratory abnormalities and DILI) in ribociclib-treated patients. Common causative/risk factors for hepatotoxicity include: • Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver, drug-drug interactions (DDIs), and decreased drug clearance. • Alcohol abuse in patients with cirrhotic liver changes • Concomitant use of hepatotoxic medications.
Risk minimization measures	**Routine risk minimization measures**: Addressed in Section 4.2, Section 4.4, Section 4.8, and Section 5.3 of the SmPC and Section 2 of PL. **Additional risk minimization measures**: None

Table 13-4 Important identified risk - QT interval prolongation

Evidence for linking the risk to the medicine	In vivo cardiac safety studies in dogs demonstrated a signal for QT prolongation at an exposure expected to be achieved in patients following the dose of 600 mg with the potential to induce incidences of PVCs at higher exposure levels (approximately 5-fold the achieved clinical Cmax). There were no effects on heart rate, blood pressure, core body temperature, or other ECG findings.
Risk factors and risk groups	Patients with history of cardiac disease, electrolyte imbalances (hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia), and concomitant intake of QT-prolonging drugs.

	The co-administration of medications that may increase the risk of QTc prolongation such as strong CYP3A4 inhibitors; and medications that have a known risk for QT prolongation.
Risk minimization measures	**Routine risk minimization measures**: Addressed in Section 4.2, Section 4.4, Section 4.5, Section 4.8, Section 5.1 and Section 5.3 of the SmPC and Section 2 of PL. **Additional risk minimization measures:** None

Table 13-5 Important identified risk – Reproductive Toxicity

Evidence for linking the risk to the medicine	Based on findings in animals and mechanism of action, ribociclib can cause fetal harm when administered to a pregnant woman. Ribociclib caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below and 1.5 times the human clinical exposure based on area under the curve (AUC). Based on animal studies, ribociclib may impair fertility in males of reproductive potential.
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with ribociclib through pregnancy.
Risk minimization measures	**Routine risk minimization measures**: Addressed in Section 4.4, Section 4.6 and Section 5.3 of the SmPC and Section 2 of PL. **Additional risk minimization measures**: None

Table 13-6 Important Potential risk - Renal toxicity

Evidence for linking the risk to the medicine	Reversible degeneration of the kidney tubular epithelial cells has been observed in the 15-week rat toxicity study. Cases of creatinine increase have been reported in clinical studies. The endogenous marker, cystatin C, was measured to further investigate renal function, and no obvious changes in cystatin C levels were observed following a single 400 mg dose of ribociclib, suggesting ribociclib does not cause direct renal toxicity (Study A2116 Interim report Part 1 dated 02-Feb-2018).
Risk factors and risk groups	Patients with severe renal dysfunction Patients with severe dehydration.
Risk minimization measures	**Routine risk minimization measures** Addressed in Section 4.2, Section 4.8 and Section 5.2 of the SmPC **Additional risk minimization measures**: None

Table 13-7 Missing information - Safety in Japanese patients

Risk minimization measures	**Routine risk minimization measures**: None **Additional risk minimization measures**: None

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

NATALEE (CLEE011O12301C) study is mentioned in NATALEE (CLEE011O12301C) study is mentioned in Table 13-8.

Table 13-8 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
NATALEE (CLEE011O12301C)	The purpose of this trial is to evaluate the effect of the addition of ribociclib to standard adjuvant endocrine therapy on invasive disease-free survival in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative anatomic stage Group III, IIB or a subset of Stage IIA early breast cancer.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Kisqali.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Checklist

Liver Injury version 3.0 May-2021

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

1. Diagnosis and date of diagnosis_____

2. Did the patient present with any of the following signs or symptoms? **Check all that apply:**

- ☐ Jaundice
- ☐ Dark urine
- ☐ Pale stool
- ☐ Ascites
- ☐ Fever
- ☐ Fatigue
- ☐ Asterixis (flapping tremor)
- ☐ Altered mental status
- ☐ Abdominal pain (specify location)
- ☐ Pruritus
- ☐ Nausea
- ☐ Caput medusa
- ☐ Gynecomastia
- ☐ None
- ☐ Bleeding (specify location)
- ☐ Spider angiomata
- ☐ Peripheral edema
- ☐ Muscle wasting
- ☐ Anorexia
- ☐ Variceal Bleeding
- ☐ Fetor hepaticus
- ☐ Other (specify)

3. Were any of the following diagnostic tests performed?

►If yes, please specify the dates and results including reference range and pre- and post- treatment values:

- ☐ Liver function tests
- ☐ Serology & PCR testings for Hepatitis A, B, C &/or E virus
- ☐ Autoantibody tests
- ☐ Abdominal or hepatobiliary ultrasound (with or without Doppler's)
- ☐ Abdominal CT scan / MRI
- ☐ Liver biopsy
- ☐ Liver transplant (planned or completed)
- ☐ Other (specify)
- ☐ None

4. Does the patient have a history of any of the following prior to the start of the suspect drug? **Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details:**

- ☐ Previously elevated liver enzymes
- ☐ Hepatitis
- ☐ Other hepatobiliary disease or dysfunction
- ☐ Autoimmune disease (specify type)
- ☐ Active or chronic pancreatitis
- ☐ Diabetes mellitus (Type I or II)
- ☐ Non-alcoholic steatohepatitis
- ☐ Cirrhosis
- ☐ Ascites
- ☐ Spider angiomata
- ☐ None
- ☐ Tattoos
- ☐ Transfusion or blood product administration
- ☐ Gilbert's disease
- ☐ Alcohol intake (quantify if possible)
- ☐ Drug abuse
- ☐ Foreign travel
- ☐ Active gall bladder disease
- ☐ Portal hypertension
- ☐ Variceal bleeding/esophageal varices
- ☐ Thrombocytopenia
- ☐ Other (specify)

5. Has the patient recently (i.e., within the past 6 months) taken any of the following? **Check all that apply:**

- ☐ Sulfonamides
- ☐ Furosemide
- ☐ ACE Inhibitors

☐ Amoxicillin / clavulanic acid	☐ NSAIDS (e.g., ibuprofen)	☐ Estrogens (oral contraceptives)
☐ Metronidazole	☐ Acetaminophen/Paracetamol	☐ Amiodarone
☐ COX II inhibitors(e.g. celecoxib)	☐ Tetracycline	☐ Steroids
☐ Thiazide diuretics	☐ 6-Mercaptopurine	☐ Statins
☐ Valproic acid	☐ Methotrexate	☐ Other (specify)
☐ None		

QT interval prolongation

QT Interval prolongation or Torsades de Pointes Targeted Follow-up Checklist version 3.0 Jan-2021

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Patient:

Age: _____ Gender: _____ Height (cm):_____ Weight (kg): _____

Event Description:

What were the maximum QT measurements, and which QT formula was used?
QT _____msec QTc _____msec Fridericia ☐ Bazett ☐ Other/Unknown ☐

What were the patient's pretreatment baseline QT and QTc values, and which QT formula was used?
QT _____msec QTc _____msec Fridericia ☐ Bazett ☐ Other/Unknown ☐

At the time of the maximum QTc:

Were triplicate ECGs collected?	Yes ☐	No ☐
Were the QT values confirmed by manual over read?	Yes ☐	No ☐
Was the subject symptomatic?	Yes ☐	No ☐

Comments _____

If no correction formula was used provide the Heart Rate at the maximum QT interval _____ beats per minute

At the time of the maximum QTcF -		Yes	No
Was arrhythmia present at the time of the QT measurement?		☐	☐
Was there any evidence of U waves?		☐	☐
Was there evidence of abnormal or biphasic T waves?		☐	☐
Was a rhythm strip obtained?		☐	☐
Were any of the following symptoms present?			
	Palpitations	☐	☐
	Syncope	☐	☐
	Lightheadedness	☐	☐
	Cardiac arrest	☐	☐

Diagnostic tests (if Yes, please attach copy/copies of each):

ECG recording and report showing the prolonged QT interval	☐	☐
Pre-event ECG recordings	☐	☐

Post-event ECG recordings ☐ ☐
Results of echocardiogram and/or other cardiac studies ☐ ☐
Was the patient seen by a cardiologist? ☐ ☐
Is a Cardiologist / expert consultant report available? ☐ ☐
If yes, provide diagnostic and relevant results:

_____

_____

_____

Were any electrolyte / blood chemistry results abnormal? ☐ ☐
If yes, provide the values at the time of the event:

☐ Potassium: level_____ ☐ Magnesium: level_____ ☐ Calcium: level_____

Were arterial blood gases done? ☐ ☐
If so, provide the results? PO2_____PCO2 _____ pH _____ HCO^3_____ BE _____
Did the patient have an acid-base abnormality? ☐ ☐
If so, what was the pH? _____

Relevant medical history (including current and pre-existing conditions)

Does the patient have a history of any of the following risk factors? Please specify condition and date of onset:

	Yes	No	Onset (dd/mm/yyyy)
Coronary ischemia, myocardial infarction	☐	☐	_____
Cardiomyopathy	☐	☐	_____
Cardiac Failure	☐	☐	_____
Cardiac Failure	☐	☐	_____
Valvular Heart disease	☐	☐	_____
High degree AV block heart block	☐	☐	_____
Syncope	☐	☐	_____
Hypothyroidism	☐	☐	_____
Hyperthyroidism	☐	☐	_____
Bradycardia	☐	☐	_____
Congenital QT prolongation (e.g.: Romano-Ward syndrome)	☐	☐	_____
Other relevant condition/s: _____	☐	☐	_____

Positive family history of QT prolongation, Deafness or Sudden death? ☐ ☐_____

QT prolonging medication at the time of the QT event:

Please refer to QTdrugs.org or CredibleMeds.org for current list of drugs known to prolong QT as this list is continually updated.

Yes No Onset (dd/mm/yyyy)

Did the patient concurrently receiving any drugs that can prolong QT interval? ☐ ☐
If yes, please indicate all that apply below:

Drug nameStart dateEnd date (if known)Dosage (mg/day)

1._____

2._____

3._____

4._____

5._____

6._____

7._____

☐ Other (*Please refer to* www.QTdrugs.org for more information):_____

_____

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Annex 6 - Details of proposed additional risk minimization activities (if applicable)

No additional risk minimization activities are proposed for any of the safety concerns.