15 November 2018
EMA/888562/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kisqali

International non-proprietary name: ribociclib

Procedure No. EMEA/H/C/004213/II/0004

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

Ae0-t	The amount of unchanged compound (or defined metabolite) excreted into the urine from time 0 to a defined point in time. In reports, the time t should be specified and the exact forms, e.g. Ae0-120hr etc, should be used for reporting (mass).
AI	Aromatase inhibitor
ANC	Absolute neutrophil count
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
AUClast	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC0-t	Area under the plasma concentration-time curve (AUC) from time zero to time 't' where t is a defined time point after administration
AUC0-6h	Area under the curve from time zero to 6 h
AUC0-24h	Area under the curve from time zero to 24 h
CI	Confidence interval
CLr	Renal clearance (volume x time-1)
CL/F	Apparent oral clearance
Cmax	Maximum plasma concentration following drug administration
Cmax,ss	Maximum plasma concentration following drug administration at steady state
Ctrough	Trough plasma concentration
Ctrough,avg,ss	Average trough concentration at steady state
Ctrough,ss	Trough plasma concentration at steady state
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DI	Dose intensity
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
E-R	Exposure-response
ESRD	End stage renal disease
GMR	Geometric mean ratio
HER2	Human epidermal growth factor receptor 2
hERG	Human ether-à-go-go-related gene
HR	Hormone receptor
IC50	Inhibitory concentration
LFT	Liver function test
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LHRH	Luteinizing hormone-releasing hormone
LLOQ	Lower limit of quantification
MAA	Marketing authorization application
MCMC	Markov Chain Monte Carlo
MR	Metabolic ratio
NCA	Non-compartmental analysis
NSAIs	Non-steroidal aromatase inhibitors
pcVPC	Prediction-corrected visual predictive check
PBPK	Physiologically-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics

popPK	Population pharmacokinetics
Racc	Accumulation ratio
SS	Steady state
T1/2	Terminal elimination half-life
T1/2,acc	Effective half-life based on drug accumulation at steady state
Tmax	The time to reach the maximum concentration after drug administration
TTR	Time to response
VPC	Visual predictive check
Vz/F	Apparent volume of distribution during the terminal elimination phase following extravascular administration

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 30 May 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant for Kisqali; in pre- or perimenopausal women, the endocrine therapy (aromatase inhibitor or fulvestrant) should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist. The extension to the indication is based upon data from study CLEE011E2301 (A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer) and study CLEE011F2301 (A randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who have received no or only one line of prior endocrine treatment). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and to make an administrative update to the Estonian and Latvian local representatives addresses in the Package Leaflet. An updated RMP version 2.0 was submitted as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant sought Scientific Advice at the CHMP pertaining to clinical aspects (EMEA/H/SA/2912/1/2014/II).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 May 2018
Start of procedure:	23 June 2018
CHMP Rapporteur Assessment Report	28 August 2018
PRAC Rapporteur Assessment Report	24 August 2018
PRAC members comments	29 August 2018
Updated PRAC Rapporteur Assessment Report	30 August 2018
PRAC Outcome	6 September 2018
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 September 2018
Request for supplementary information (RSI)	20 September 2018
PRAC Rapporteur Assessment Report	22 October 2018
PRAC members comments	24 October 2018
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	31/10/2018
CHMP Rapporteur Assessment Report	01/12/2018
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	08/11/2018
Opinion	15/11/2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Kisqali, in combination with Fulvestrant, is proposed for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

2.1.2. Epidemiology

Breast cancer is the second most common cancer in the world and the most frequent among women. An estimated 1.67 million women were diagnosed with breast cancer worldwide in 2012 (representing around 25% of all cancers in women) and approximately 522,000 deaths were recorded[1]. In EU there were 3.7 million new cases of breast cancer, and 1.9 million cancer deaths and 9.7 million people living with cancer (within 5 years of diagnosis) in 2012[2].

2.1.3. Biologic features

Breast cancer is a molecularly diverse disease with several clearly defined molecular subgroups[3]. There are three well described subtypes: hormone receptor (HR) positive (estrogen receptor/progesterone receptor positive), HER-2 positive and triple negative breast cancer (TNBC). The predominant subset is HR-positive, HER2-negative disease. The expression of these biological markers in breast cancer is correlated with prognosis and response to treatment, and therefore plays an important role in treatment decisions.

2.1.4.Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment. Clinical examination includes bimanual palpation of the breasts and locoregional lymph nodes and assessment for distant metastases (bones, liver and lungs; a neurological examination is only required when symptoms are present)[4].

Of the new breast cancer cases diagnosed worldwide each year, roughly 60% to 65% are HR-positive, 20% to 25% are HER2-positive, and 15% to 18% are triple-negative (Estrogen receptor-negative, Progesterone receptor-negative, HER2-negative)[5].

Metastatic breast cancer is an incurable disease with a median overall survival of 2~3 years and a 5-year survival of only~25%. Median overall survival in patients with advanced breast cancer patients with tumours expressing the estrogen receptor (ER) but not the human epidermal growth factor receptor 2 is approximately 2.5 to 4 years.

2.1.5.Management

Locally advanced or metastatic breast cancer patients derive benefit mainly from systemic treatments. Endocrine therapy remains the therapeutic backbone for the treatment of HR+ cancers. For postmenopausal women with HR+ advanced breast cancer, the endocrine therapy options include, but are not limited to, selective estrogen receptor modulators (SERM; e.g. tamoxifen), estrogen receptor antagonists (e.g. fulvestrant), selective non-steroidal aromatase inhibitors (NSAI; e.g. anastrozole and letrozole) and steroidal aromatase inhibitors (e.g. exemestane). TTP/PFS in the range of 5- 15 (20) months is typical in endocrine therapy trials in the postmenopausal population (Kümler ESMO Open 2016). Endocrine therapy may be given in first, second or later lines of therapy for advanced breast cancer[6,7].

Recently, cyclin dependent kinase (CDK) 4/6 inhibitors were approved in this setting. Palbociclib (Ibrance), ribociclib (Kisqali) and abemaciclib (Verzenios) are authorised as an add-on to endocrine therapy. Palbociclib and abemaciclib are both approved in combination with AI or fulvrestrant while Kisqali is approved in combination with AI.

[1] Ferlay et. al., Int J Cancer, 2012
[2] GLOBOCAN Breast Cancer 2012
[3] Perou et al 2000
[4] ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
[5] Finn et al 2015
[6] ESO-ESMO 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2)
[7] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology

Progressive disease ultimately develops in all patients, either as early failure to respond to endocrine therapy (primary or de novo resistance) or as relapse/progression following an initial response (acquired resistance). According to treatment guidelines, chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance[2,3]. Single agent chemotherapy is preferred, as no overall survival benefit has been demonstrated for combinations. Anthracyclines or taxanes would usually be considered 1st line, if not administered in the (neo) adjuvant setting. Capecitabine and vinorelbine are options for patients that have received anthracyclines or taxanes, and can thus be used in the 1st or 2nd line metastatic setting. Eribulin is approved for breast cancer patients who have progressed after ≥1 chemotherapeutic regimen for advanced disease, and have previously received an anthracycline and a taxane.

About the product

Ribociclib is a selective inhibitor of cyclin dependent kinase (CDK) 4 and 6, resulting in 50% inhibition (IC50) values of 0.01 (4.3 ng/ml) and 0.039 µM (16.9 ng/ml) in biochemical assays, respectively. These kinases are activated upon binding to D cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

Ribociclib was approved on 22 August 2017 and is indicated in combination with an aromatase inhibitor for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy. Authorisation was based on the results of a randomised, double blind, placebo controlled, multicentre phase III clinical study (CLEE011A2301/MONALEESA-2) conducted in the treatment of postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone. This study showed statistically significant improvement in PFS in patients receiving Kisqali plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (hazard ratio of 0.556, 95% CI: 0.429, 0.720, one sided stratified log rank test p value 0.00000329).

With the present variation, the applicant applied for an extension of indication to include the combination with fulvestrant and extend the population to premenopausal women and men:

"Kisqali ~~in combination with an aromatase inhibitor~~ is indicated for the treatment of <u>patients</u> ~~postmenopausal women~~ with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer <u>in combination with an aromatase inhibitor or fulvestrant</u> ~~as initial endocrine based therapy~~.

<u>In pre or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone releasing hormone (LHRH) agonist</u>."

The recommended indication is as follows:

"Kisqali is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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."

The recommended dose is 600 mg (three 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. The treatment

should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Kisqali should be used together with 2.5 mg letrozole or another aromatase inhibitor or with 500 mg fulvestrant.

When Kisqali is used in combination with an aromatase inhibitor, the aromatase inhibitor should be taken orally once daily continuously throughout the 28 day cycle. Please refer to the Summary of Product Characteristics (SmPC) of the aromatase inhibitor for additional details.

When Kisqali is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the SmPC of fulvestrant for additional details.

Treatment of pre- and perimenopausal women with the approved Kisqali combinations should also include an LHRH agonist in accordance with local clinical practice.

Type of Application and aspects on development

Scientific Advice was received regarding study CLEE011E2301/MONALEESA-7, adopted by CHMP in November 2014 (EMEA/H/SA/2912/1/2014/II) and pertaining to the following points:

- The overall study design, to study premenopausal women with HR+, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced breast cancer, treated with ribociclib or placebo + NSAI/tamoxifen + goserelin was accepted.
- PFS was accepted, if BIRC indicates that there is no relevant bias in the investigator assessment of progression, it was considered appropriate to use investigator data in the primary analysis.

  It was assumed that patients will be followed not only for survival, but also for PFS2 in line with the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)
- The planned final analysis was to be conducted after 329 events. The second interim analysis for efficacy was discussed with regard to risk of not having a stable result (too few events in the control arm; at an event rate of about 60% in the control group, data were considered sufficiently likely to be stable.)
- Comments were made on the proposed OS-analyses. In the advice given it was pointed out that it appeared less wise to define the “final” OS analysis at an event rate slightly higher than 50% of the events in the long run.

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH submitted non-clinical data from new pharmacology studies as well as from previously submitted ones. Furthermore, the results of a new female fertility and early embryonic development study and from an additional 1 week repeat dose toxicity study in rats were presented.

2.2.2. Pharmacology

Primary pharmacodynamic studies

Combination of ribociclib with letrozole in a primary ER+ breast cancer patient derived xenograft model in mice (RD-2015-00085) (see EPAR Kisqali)

In a primary ER+ breast cancer xenograft model (HBCx-34) derived from a patient tumor, ribociclib (75 mg/kg/day) in combination with letrozole (at 2.5 mg/kg/day), a non-steroidal aromatase inhibitor (NSAI), both dosed orally every day for 55 days, induced greater tumour growth inhibition than each agent alone. The combination of ribociclib and letrozole demonstrated statistically significant ($p<0.001$ compared with vehicle controls) antitumor activity with complete tumour growth inhibition, and 2 out of 10 partial and 2 out of 10 complete tumour regressions. Tumour regrowth was delayed for 33 days after stopping dosing (see EPAR Kisqali).

Combination of ribociclib with tamoxifen or ribociclib with fulvestrant in a primary ER+ breast cancer tumour xenograft model (studies reports RD-2015-00701 and RD-2016-00052)

Combination of ribociclib with other endocrine therapies used in breast cancer treatment, namely tamoxifen, a selective ER modulator (SERM); or fulvestrant, an ER antagonist, was also evaluated.

Combination of ribociclib (75 mg/kg/day) and tamoxifen (1 mg/kg/day) was assessed in an ER+ breast cancer patient derived xenograft model (HBCx-34). When dosed orally once daily for 55 days, the combination treatment induced a very strong and statistically significant ($p<0.001$ compared with vehicle controls) tumour growth inhibition with 7 out of 10 partial tumour regressions and 3 out of 10 complete tumour regressions (study report RD-2015-00701).

Compared to each agent alone, the combination of ribociclib plus tamoxifen resulted in an enhanced antitumor activity with sustained tumour regression and was well tolerated. In the ZR751 ER+ human breast cancer xenograft model, combination of ribociclib (75 mg/kg/day) with fulvestrant (5 mg/kg, once weekly) induced complete tumour growth inhibition (study report RD-2016-00052).

Pharmacodynamic effect of combination treatments of ribociclib plus tamoxifen or ribociclib plus fulvestrant (study report RD-2017-00236)

Pharmacodynamic markers of ribociclib namely of phospho-pRb and total pRb were assessed in ER+ human breast cancer cell lines, T47D, ZR-75-1 and EMF19, and in ZR-75-1 xenograft tumor samples.

After 24 hours of treatment, ribociclib reduced phospho-pRb, tamoxifen and fulvestrant as single agents had no or very minor effects dependent on the cell lines; however, the inhibition effect of the combinations was stronger. After 6 days, only combination treatment maintained a strong suppression of phospho-pRb, while single agents including ribociclib only had partial suppression. A reduction of total pRb protein was also detectable under the same conditions, although it appeared less pronounced.

After 6 days, only the combinations maintained a strong suppression of phospho-pRb across all cell lines, while pRb phosphorylation partially recovered in samples treated with ribociclib alone.

The effects of the same treatments as above in ZR-75-1 xenograft tumour samples showed no consistent effect of single agent treatments observed in ZR-75-1 tumours after 6 days of treatment, while combinations strongly reduced phospho-pRb with a concomitant decrease in total pRb.

Secondary pharmacodynamic studies

Ribociclib and LEQ803, a prominent metabolite of ribociclib, were assessed for their off-target activity on G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes. For ribociclib, activities were found on phosphodiesterase PDE4d (IC50 = 0.59 µM, n=2), rat vesicular monoamine transporter VMAT2 (IC50 = 6.3 µM, n=2), orexin-2 receptor (70% inhibition at 10 µM) and apelin receptor (54% inhibition at 10 µM). For LEQ803, activities were found on phosphodiesterase PDE4d (IC50 = 0.6 µM), serotonin 5HT3 channel (IC50 = 2.63 µM), neuronal nicotinic alpha 2 channel (IC50 = 5.7 µM), cannabinoid CB1 receptor (IC50 = 28 µM), peripheral rat imidazoline I2 receptor (71% inhibition at

10 µM), rabbit monoamine transporter VMAT2 (84% inhibition at 10 µM) and rat brain sodium channel site II (70% inhibition at 10 µM).

Newly presented data[8] reported central nervous system penetration of ribociclib in non-tumor bearing mice and mice bearing orthotopic pediatric brain tumors. Taking into consideration these newly published data and in order to assess the effects of ribociclib or LEQ803 from interactions with targets expressed in the central nervous system, the free brain concentrations had to be estimated. Using a one compartment plasma model with two-compartment tumor model fitted to all data using NONMEM (Patel 2016) ribociclib free concentration in the brain were estimated to be 12% of the free concentration in plasma. At therapeutic doses (600 mg), mean free plasma concentration of ribociclib was 1.2 µM (as reported in the summary of clinical pharmacology of the original dossier), corresponding to a free brain concentration of 0.144 µM. With the exception of PDE4 (ratio IC50/brain free Cmax = 4.1), exposure margins were >20 for all the previously identified secondary targets.

2.2.3. Toxicology

Table 1: Overview of toxicology studies

Study type	Species and strain	Method of administration	Duration of dosing	Doses (mg/kg[a])	GLP compliance	Testing facility[b]	Study number	TK collected
Repeated dose toxicity	Rat / Han Wistar	oral, gavage	7 days	600, 1200	no	Novartis, EH	[1770546]	yes
Reproductive and development toxicity:	Rat / Han Wistar	oral, gavage	14 days prior to cohabitation, during cohabitation continuing through day 6 pc (female)	50, 150, 300 NOAEL: F0 females: 300 F1 litters: 300	yes	CRL, Canada	[1570198]	no

[a] = Unless otherwise specified.
NOAEL = No Observed Adverse-Effect Level
CRL = Charles River Laboratories Preclinical Services Montreal, Senneville, Quebec, Canada
pc = postcoitum

Repeat dose toxicity

In order to better estimate an appropriate high dose in female rats for the two year carcinogenicity study an additional female rat toleration study was conducted (study 1770546).

In this non-GLP study, ribociclib was administered daily orally to groups of 5 female rats at dosages of 600 and 1200 mg/kg/day during a 7-day period.

Hematology changes were consistent with minimal to mild suppression of hematopoiesis related to CDK4/6 inhibition and to an acute phase protein response (lower albumin concentration and lower albumin:globulin ratio), slightly higher creatinine and/or lower cholesterol concentration.

Histopathological findings were observed at $\geq$ 600 mg/kg/day in the gastrointestinal tract (ulceration of the epithelium and submucosal infiltration of neutrophils in stomach, duodenum, and ileum) which macroscopically correlated with raised or ulcerated areas in the stomach; the liver (bile duct epithelium vacuolation and reduced inflammatory cell infiltrations), lung (increased alveolar macrophages and reduced inflammatory cell infiltrations), spleen (reduced extramedullary hematopoiesis), and mesenteric lymph node (histiocytosis and reduced germinal center development).

[8] Patel Y, 2016

The macroscopic and microscopic changes in the gastrointestinal tract were clearly dose dependent and indicative of poor local tolerance of ribociclib at ≥ 600 mg/kg/day. While slight effects on the gastrointestinal tract have been seen in a 2-week dog toxicity study, they were absent in the 15- and 27-week toxicity studies where females rats were treated up to 300 mg/kg/day. Similar macroscopic changes have also been observed in the rat embryo-fetal development study at 1000 mg/kg/day.

Reproduction toxicity

Fertility and early embryonic development study in the rat (study 1570198)

The purpose of this GLP study (Study 1570198) was to test for potential toxic effects/disturbances resulting from ribociclib treatment of female Wistar Hannover (Crl:WI [Han]) rats before cohabitation, through mating and implantation. This study evaluated ICH Harmonised Tripartite Guideline stages A and B of the reproductive process and was intended to detect effects on the estrous cycle, tubal transport, implantation, and development of preimplantation stages of the embryos of females and permit detection of functional effects (e.g., effects on libido) that may not be detected by histological examinations of female reproductive organs.

Ribociclib formulated in 0.5% (w/v) methylcellulose 400 cPs, aqueous solution, was administered by oral gavage (5 mL/kg) to 3 groups of 24 rats at dose levels of 50, 150 and 300 mg/kg/day for 14 days prior to cohabitation, during cohabitation and through day 6 postcoitum. Another group of 24 female rats received the vehicle and served as controls. The rats were obtained from Charles River, Kingston, New York, USA. The females were 11 to 12 weeks of age and weighed 186 to 222 g at the start of dosing. The following parameters were evaluated: cage side observations, detailed clinical examinations on days of body weight assessments (twice weekly during the premating period and on days 0, 3, 6, 9, and 13 postcoitum for mated females); twice weekly food consumption, estrous cycling (for 14 consecutive days beginning with the first day of dosing), macroscopic observations and ovarian and uterine examinations on day 13 postcoitum.

There was no ribociclib-related mortality, nor any adverse clinical signs.

Body weight parameters and food consumption were unaffected by the administration of ribociclib. There were no ribociclib-related gross pathological findings.

Administration of ribociclib had no effect upon estrous cycles or parental performance (mean day to mating, the mating, fertility, gestation indices or conception rate). The ovarian and uterine parameters assessed were not affected by the administration of ribociclib.

2.2.4. Ecotoxicity / environmental risk assessment

The planned extension of the Kisqali indication was considered in the marketing forecast provided at the time of initial marketing authorization in the ERA. As part of the present application, the MAH provided an update ERA with updated forecast figures. However these did not change significantly from the estimates used in the initial Kisqali ERA.

2.2.5. Discussion on non-clinical aspects

The MAH presented data on primary pharmacodynamics supporting the combination of ribociclib with tamoxifen or fulvestrant.

In vivo antitumour activity of ribociclib in combination with fulvestrant was assessed in immune deficient mice bearing the ZR751 ER+ human breast cancer xenografts and the combination with fulvestrant resulted in complete tumour growth inhibition. The SmPC has been updated to reflect this new data and to clarify that in the preclinical models tested so far, intact pRb was required for ribociclib activity (see SmPC section 5.1).

The MAH also analysed the possibility for off target activity in the CNS with a number of targets previously identified in a conventional secondary pharmacology screen. Based on mouse data on CNS distribution in mice, this analysis showed that centrally-mediated untoward effects resulting from interactions with targets expressed in the central nervous system are unlikely to develop in humans.

The MAH explored the possibility to use higher doses than those tested in the pivotal repeat-dose toxicity studies. At the highest dose in these studies, there was limited toxicity and the exposure at the high dose in female rats was similar to clinical exposure. It is agreed that the findings in the 1 week rat study suggest that a higher dose (>300 mg/kg) is unlikely to be tolerated in a longer study.

The effects in the spleen, mesenteric lymph node, liver and lung observed in this study were in accordance to previous repeat dose toxicity studies and correlated well with the findings in clinical pathology.

A new study on fertility and embryonic development in female rats was presented. In this study in female rats, ribociclib did not affect reproductive function, fertility or early embryonic development at any dose up to 300 mg/kg/day (which is likely at an exposure lower than or equal to patients' clinical exposure at the highest recommended dose of 600 mg/day based on AUC) (see SmPC section 5.3).

No toxicokinetic study was performed. However exposure at the high dose 300 mg/kg was similar to clinical exposure in the rat repeat-dose toxicity studies.

Data on developmental and reproductive toxicity were assessed within the initial MAA procedure (see below). Considering the proposed indication is now covering pre-menopausal women, the SmPC sections 4.6 and 5.3 have been updated to reflect adequate information with regards to pregnancy, breast-feeding and fertility.

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the rats or rabbits. Following prenatal exposure, increased incidences of post-implantation loss and reduced foetal weights were observed in rats. Reduced foetal weights were accompanied by skeletal changes considered to be transitory and/or related to the lower foetal weights. In rabbits, ribociclib was teratogenic at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC (see EPAR Kisqali and SmPC section 5.3). There were adverse effects on embryo-foetal development in rabbits as evidenced by increased incidences of foetal abnormalities (malformations and external, visceral and skeletal variants) and foetal growth (lower foetal weights). These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60 mg/kg), extra/rudimentary thirteenth ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-foetal mortality (see EPAR Kisqali).

Women of childbearing potential who are receiving Kisqali should use effective contraception (e.g. double-barrier contraception) during therapy and for at least 21 days after stopping treatment with Kisqali (see SmPC sections 4.4 and 4.6).

There are no adequate and well-controlled studies in pregnant women. Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman. Kisqali is not recommended during pregnancy and in women of childbearing potential not using contraception (see SmPC section 4.3).

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 (see SmPC section 5.3). These effects can be linked to a direct anti proliferative effects on the testicular germ cells resulting in atrophy of the seminiferous tubules (see SmPC section 5.3). A complete reversibility was not demonstrated. There are no clinical data available regarding effects of ribociclib on fertility. However, based on the testis toxicity ribociclib may impair fertility in males of reproductive potential (see EPAR Kisqali and SmPC section 4.6).

Ribociclib and its metabolites readily passed into the milk of lactating rats. The exposure to ribociclib was higher in milk than in plasma (see EPAR Kisqali). 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. Patient receiving Kisqali should not breast-feed for at least 21 days after the last dose (see SmPC section 4.6).

The period of 21 days after treatment with Kisqali is discontinued is considered acceptable as it corresponds to approximately 5 ribociclib half-lives.

The planned extension of the Kisqali indication was considered in the marketing forecast provided at the time of initial marketing authorization in the ERA. The MAH provided an update ERA which included an updated market forecast. No new ERA study was provided. All PEC/PNEC ratios remained ≤1. In conclusion, while the new prediction resulted in a higher market forecast, the new calculations did not result in any suggestion of an environmental risk.

2.2.6. Conclusion on the non-clinical aspects

The non-clinical data presented are considered sufficient to support of this extension of indication.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of ribociclib. Considering the above data, ribociclib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Two studies were performed in support of this extension of indication (Table 2).

Table 2. Overview of clinical studies

Protocol No., Study Dates, Countries & Publication References	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage
protocol: [CLEE011E2301] countries: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Colombia, France, Germany, Greece, Hong Kong, Hungary, India, Italy, Republic of Korea, Lebanon, Malaysia, Mexico, Poland, Portugal, Russian Federation, Saudi Arabia, Singapore, Spain, Switzerland, Taiwan province of China, Thailand, Turkey, United Arab Emirates and United States **start:** 20-Nov-2014 **end:** ongoing **publ.:** None	**design, goal & population:** A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer **evaluations:** **efficacy:** PFS from Investigator's review of radiology data using RECIST version 1.1 criteria, OS (Overall survival). Overall response rate (ORR), Clinical benefit rate (CBR), time to response (TTR), duration of response (DoR) and Eastern Cooperative Oncology Group (ECOG) performance status. (CR) complete response or (PR) partial response **patient reported outcomes:** EORTCQLQC30 questionnaire along with the breast module (QLQ-BR23) and EQ-5D-5L. **safety:** (AEs), vital signs, body weight, physical examinations, ECGs, hematology, biochemistry and urinalysis.	Enrollment complete **total:** 672 (388w, 19b, 198a, 67o) **age:** 25-58 (43.1) **groups:** 2 (672f) **Group 1:** 335 (335f) **Group 2:** 337 (337f)	**form(s):** hard gelatin: ribociclib matching placebo subcutaneous implant: goserelin tablets: tamoxifen letrozole anastrozole **duration:** until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. **doses:** Ribociclib 600 mg, once daily 3 weeks on/1 week off schedule + goserelin (3.6 mg once a month) + either tamoxifen (20 mg once daily) or a NSAI (letrozole 2.5 mg or anastrozole 1 mg once daily). Placebo 600 mg, once daily 3 weeks on/1 week off schedule + goserelin (3.6 mg once a month) + either tamoxifen (20 mg once daily) or a NSAI (letrozole 2.5 mg or anastrozole 1 mg once daily).

protocol: [CLEE011F2301] Interim analysis **countries:** Australia, Austria, Belgium, Bulgaria, Canada, Colombia, Czech Republic, Denmark, France, Germany, Hungary, Italy, Jordan, Republic of Korea, Lebanon, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russian federation, Singapore, Spain, Sweden , Switzerland, Thailand, Turkey, United Kingdom, United States. **start:** 09-Jun-2015 **end:** ongoing **publ.:** none	**design, goal & population:** A randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. **evaluations:** **efficacy:** PFS from Investigator's assessment of radiology data using RECIST version 1.1 criteria, (Overall survival). Overall response rate (ORR), Clinical benefit rate (CBR), time to response (TTR), duration of response (DoR) and Eastern Cooperative Oncology Group (ECOG) performance status. EORTCQLQC30 questionnaire along with the EQ-5D-5L and BPI-SF.	Enrollment complete **total:** 726(619w, 5b, 63a, 39o) **age:** 31-89 (63) **groups:** 2 (726f) **Group 1:** 484 (484f) **Group 2:** 242 (242f)	**form(s):** Ribociclib hard gelatin capsule Placebo hard gelatin capsule Fulvestrant im injection **duration:** until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. **doses:** Ribociclib 600 mg, once daily 3 weeks on/1 week off schedule + fulvestrant 500 mg on Days 1 and 15 of Cycle 1 (4 weeks) and on Day 1 of subsequent cycles. Placebo 600 mg, once daily 3 weeks on/1 week off schedule + fulvestrant 500 mg on
	safety: AEs, SAEs, hematology, chemistry, lipid panel, coagulation, urinalysis, height and weight, vital signs, ECG, physical examinations.		Days 1 and 15 of Cycle 1 (4 weeks) and on Day 1 of subsequent cycles.

protocol:[CLEE011X2108] Interim analysis **countries:** France, Italy, Singapore, Spain, USA **start:** 19-May-2014 **cut-off date for interim analysis:** 10-Feb-2017 **end:** ongoing **publ.:** Tolaney SM, Forero-Torres A, Boni V, et al (2017) Ribociclib + fulvestrant in postmenopausal women with HR+, HER2- advanced breast cancer (ABC) [abstract]. Cancer Res; 77(4):P4-22-12.	**design, goal & population:** A Phase Ib/II study of ribociclib (LEE011) in combination with fulvestrant and alpelisib (BYL719) or buparlisib (BKM120) in the treatment of postmenopausal women with hormone receptorpositive (HR-positive), human epidermal growth factor receptor 2 (HER2) negative locally recurrent or advanced metastatic breast cancer. Interim CSR for LEE011 (3 weeks on/1 week off regimen) plus fulvestrant treatment arm (Arm 3) **evaluations:** MTD/RP2D **efficacy:** Investigator's assessment of tumor response using RECIST version 1.1 criteria	This is an interim analysis and only provides the results for Arm 3 **total:** 13 (11w, 0b, 2a, 0o) **age:** 47-75 (59.5) **groups:** 1(13f) Ribociclib 600mg + fulvestrant 500 mg (13f)	**form(s):** capsules **duration:** There was no fixed treatment duration. Patients could receive treatment until disease progression, unacceptable toxicity occurs that precludes any further treatment and/or treatment is discontinued at the discretion of the Investigator or by patient refusal (withdrawal of consent). **doses:** Ribociclib 600 mg, once daily 3 weeks on/1 week off schedule + fulvestrant 500 mg on Days 1 and 15 of Cycle 1 (4 weeks) and on Day 1 of subsequent cycles.
	safety: AEs, laboratory evaluations (hematology, chemistry, urinalysis), ECG, vital signs. Pharmacokinetics: The PK sampling, liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay Biomarkers: tumor specimen from a previous biopsy (archival tumor specimen) or from a newly obtained tumor specimen.		

2.3.2. Pharmacokinetics

Introduction

No new information on absorption, distribution, metabolism or elimination was provided in support of this application.

The absolute bioavailability of ribociclib in humans is not known. The time to reach Cmax (Tmax) following ribociclib oral administration was between 1 and 4 hours. Ribociclib exhibited slightly over-proportional increases in Cmax and AUC across the dose range tested (50 to 1200 mg). Based on a population pharmacokinetic model, ribociclib clearance would be 24% higher at 300 mg than at the reference dose (600 mg). The apparent volume of distribution for ribociclib at steady state (Vss/F) was 1090 L. The metabolism of ribociclib appears to be mediated primarily by CYP3A4 (including formation of the major metabolite

LEQ803) and to a minor extent by FMO3 and (extra-hepatic) FMO1 (including formation of the major metabolite CCI284). The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 l/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. In vitro and in vivo studies indicated ribociclib is eliminated primarily via hepatic metabolism. Ribociclib and its metabolites are eliminated mainly via faeces, with a small contribution of the renal route (see EPAR Kisqali).

In support of this application the MAH provided the following information:

- Assessment of PK of ribociclib and/or its combination partners from Study E2301 and Study F2301.

- Assessment of PK of ribociclib from study X2108 (limited data not shown)

- Assessment of drug-drug interaction (DDI) potential between ribociclib and its combination partners in Study E2301 (anastrozole, letrozole or tamoxifen) and F2301 (fulvestrant).

- Updated evaluation of covariate effects of intrinsic and extrinsic factors on ribociclib PK based on data in Study E2301, Study F2301, and data included in the original MAA.

Pharmacokinetic data analysis

Non-compartmental analysis

Method

The methods of studies E2301, F2301 and X2108 are described in details under the section on clinical efficacy.

In study E2301, ribociclib, tamoxifen, letrozole and anastrozole exposure parameters at C3D15 (Cmax, Ctrough and AUC (0-24h for tamoxifen and 0-6h for NSAI)) were assessed (co-administered with ribociclib or placebo) to evaluate the impact of ribociclib on each substance pharmacokinetics (PK). Additionally, cycle 1 and 3, day 15 and plasma concentration of LEQ803 (major metabolite of ribociclib) were assessed at times 0 and 2 hours (i.e. Ctrough and 2 hours post dose).

In study F2301, pharmacokinetic blood samples were obtained from patients for the analysis of ribociclib and LEQ803. Patients were assigned to the sparse PK collection group (approximately the first 150 patients enrolled) or the trough PK collection group (all remaining patients). For sparse PK sampling of ribociclib/placebo, blood samples were collected pre-dose on Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15, and post-dose on Cycle 1 Day 15 and Cycle 2 Day 15 at 2, 4 and 6 h. For trough PK sampling, blood samples were collected pre-dose on Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15.

The PK analysis set included 498 patients (74.1%) and 406 patients (55.9%) of the total number included patients (ribociclib and placebo arms) from study E2301 and F2301, respectively. From the active treatment arms, the PK analysis set included 77.6% and 83.9% of the patients from study E2301 and F2301, respectively. In study X2108, the PK analysis set included 13 patients.

Results

The Cmax, Cthrough and AUC of ribociclib, tamoxifen, letrozole and anastrozole exposure parameters reported in study E2301 at Cycle 3 Day 15, when co-administered with ribociclib or placebo, are presented in Table 3.

Ribociclib Ctrough and 2-hours post dose concentration at C1D15 and C3D15 in combination with endocrine treatment partner tamoxifen, letrozole and anastrozole from patients with evaluable samples are presented in Table 4.

In general, ribociclib concentrations in combination with tamoxifen were slightly lower than its concentrations in combination with a NSAI (letrozole and anastrozole).

Table 3. Summary of ribociclib, tamoxifen, letrozole and anastrozole PK parameters on Cycle 3 Day 15 from Study E2301 (Pharmacokinetic Analysis Set)

	Dose group and combination partner[a]	Statistics	Cmax (ng/mL)	AUC0-24h/ AUC0-6h (ng*hr/mL)[b]	Ctrough (ng/mL)
Ribociclib PK	Ribociclib plus goserelin plus tamoxifen	n	17	17	30
		Mean (SD)	1510 (1080)	22400 (19800)	425 (391)
		Geo-mean (Geo-CV%)	1290 (58.8)	17600 (74.3)	294 (176.7)
	Ribociclib plus goserelin plus letrozole	n	45	43	76
		Mean (SD)	1760 (521)	8000 (2590)	540 (307)
		Geo-mean (Geo-CV%)	1680 (30.6)	7590 (34.4)	457 (67.3)
	Ribociclib plus goserelin plus anastrozole	n	3	3	15
		Mean (SD)	2790 (1450)	13600 (6710)	485 (347)
		Geo-mean (Geo-CV%)	2570 (51.5)	12600 (48.1)	372 (109.7)
Tamoxifen PK	Ribociclib plus goserelin plus tamoxifen	n	17	17	29
		Mean (SD)	322 (102)	6580 (2300)	259 (126)
		Geo-mean (Geo-CV%)	304 (38.3)	6160 (41.4)	228 (58.6)
	Placebo plus goserelin plus tamoxifen	n	25	21	46
		Mean (SD)	154 (65.3)	3050 (1360)	113 (48.1)
		Geo-mean (Geo-CV%)	142 (43.5)	2780 (46.8)	102 (52.7)
Letrozole PK	Ribociclib plus goserelin plus letrozole	n	44	43	66
	Placebo plus goserelin plus letrozole	n	68	65	94
		Mean (SD)	131 (50.3)	733 (277)	109 (55.8)
		Geo-mean (Geo-CV%)	122 (41.3)	681 (41.3)	96.8 (55.9)
Anastrozole PK	Ribociclib plus goserelin plus anastrozole	n	3	3	15
		Mean (SD)	67.0 (6.35)	362 (37.7)	43.6 (19.8)
		Geo-mean (Geo-CV%)	66.8 (9.6)	360 (10.2)	38.5 (59.5)
	Placebo plus goserelin plus anastrozole	n	4	4	17
		Mean (SD)	53.9 (24.1)	260 (113)	32.9 (15.5)
		Geo-mean (Geo-CV%)	47.6 (71.7)	232 (69.0)	28.4 (70.4)

n=number of patients with corresponding evaluable PK parameters.
[a] Ribociclib 600 mg, tamoxifen 20 mg, letrozole 2.5 mg, anastrozole 20 mg, goserelin 3.6 mg
[b] Ribociclib AUC0-6h was measured when letrozole and anastrozole were given as combination partners in Study E2301.
PK=Pharmacokinetics; SD=standard deviation
Source: [Study E2301-CSR-Table 14.2-4.1], [Study E2301-CSR-Table 14.2-4.2], [Study E2301-CSR-Table 14.2-4.3], [Study E2301-CSR-Table 14.2-4.7], [Study E2301-CSR-Table 14.2-4.9], [Study E2301-CSR-Table 14.2-4.10], [Study E2301-CSR-Table 14.2-4.11], [Study E2301-CSR-Table 14.2-4.12], [Study E2301-CSR-Table 14.2-4.13], [Study E2301-CSR-Table 14.2-4.17], [Study E2301-CSR-Table 14.2-4.19], and [Study E2301-CSR-Table 14.2-4.20]

Table 4. Ribociclib Ctrough and two-hour post-dose concentration in patients following oral daily administration of 600 mg (3 week on/1 week off) ribociclib with tamoxifen, letrozole, or anastrozole as combination partner from Study E2301 (Pharmacokinetic Analysis Set)

Visit	Ribociclib combination partners					
	Tamoxifen 20 mg		Letrozole 2.5 mg		Anastrozole 1 mg	
	n/m	Geo-mean (Geo-CV%)	n/m	Geo-mean (Geo-CV%)	n/m	Geo-mean (Geo-CV%)
Cycle 1 Day 15 (pre-dose)	19/19	450 (55.2)	55/55	523 (68.4)	5/5	600 (79.8)
Cycle 1 Day 15 (2 hr)	24/24	1410 (39.7)	74/74	1580 (52.5)	7/7	1580 (46.8)
Cycle 3 Day 15 (pre-dose)	30/30	294 (176.7)	76/76	457 (67.3)	15/15	372 (109.7)
Cycle 3 Day 15 (2 hr)	44/44	1040 (56.1)	95/95	1340 (61.1)	21/21	1190 (134.3)

n: number of patients with evaluable values, m: number of non-zero concentrations
Zero concentrations are considered as missing in geometric mean and geometric CV% calculations
Source: Table 14.2-4.1, Table 14.2-4.2, Table 14.2-4.3

The C1D15 and C3D15 Ctrough and 2-hours post dose LEQ803 concentration (metabolite of ribociclib) were largely comparable among the combination partners suggesting no marked differences in LEQ803 exposure in presence of tamoxifen, letrozole or anastrozole (Table 5).

Table 5. Ribociclib Ctrough and two-hour post-dose concentration in patients following oral administration of 600 mg ribociclib with tamoxifen, letrozole, or anastrozole as combination partner from Study E2301 (Pharmacokinetic Analysis Set)

Visit	Ribociclib combination partners					
	Tamoxifen 20 mg		Letrozole 2.5 mg		Anastrozole 1 mg	
	n/m	Geo-mean (Geo-CV%)	n/m	Geo-mean (Geo-CV%)	n/m	Geo-mean (Geo-CV%)
Cycle 1 Day 15 (pre-dose)	19/19	86.2 (40.2)	55/55	78.6 (57.9)	5/5	44.0 (85.7)
Cycle 1 Day 15 (2 hr)	24/24	149 (39.9)	74/74	144 (51.7)	7/7	87.6 (78.1)
Cycle 3 Day 15 (pre-dose)	30/30	59.7 (93.2)	76/76	68.5 (49.7)	15/15	47.2 (92.3)
Cycle 3 Day 15 (2 hr)	44/44	138 (40.2)	95/95	132 (43.2)	21/21	101 (89.8)

n: number of patients with evaluable values, m: number of non-zero concentrations
Zero concentrations are considered as missing in Geo-mean and Geo-CV% calculations
Source: Table 14.2-4.4, Table 14.2-4.5, Table 14.2-4.6

In study F2301, the geometric mean ribociclib Ctrough (pre-dose) plasma concentration was 627 ng/mL (geometric CV%: 67.6%) on Cycle 1 Day 15 (n=253) and was similar to the geometric mean Ctrough of 553 ng/mL (geometric CV%: 80.7%) observed on Cycle 2 Day 15 (n=177) at the recommended dose of 600 mg ribociclib. The plasma concentrations observed at 2, 4 and 6 hours post dose were also similar between the two cycles. On Cycle 2 Day 15, the geometric mean pre-dose concentrations (n=155) was 555 ng/mL (geometric CV%: 85.5%). The geometric mean post dose concentrations at 2 hours (n=69) was 1450 ng/mL (geometric CV%: 84.3%), at 4 hours (n=73) was 1610 ng/mL (geometric CV%: 55.5%), and at 6 hours (n=63) was 1270 ng/mL (geometric CV%:94.2%).

In the phase Ib dose-finding study (X2108), following oral administration of the study treatment, the mean peak plasma concentrations for ribociclib were achieved approximately at 4-hour post dose, followed by a decline in concentrations over 24 hour dosing interval. Consistent with ribociclib monotherapy PK data, the geometric mean Cmax was 967 ng/mL and 1840 ng/mL for Cycle 1 Day 1 and Cycle 1 Day 21, respectively (Table 6). Exposure accumulation was observed after repeated ribociclib doses, with geometric mean accumulation ratio (Racc) for AUC0-24 of 2.18.

Table 6. Summary of primary PK parameters for ribociclib (PAS) from the Phase Ib dose-finding study X2108

Time point	Treatment	Statistics	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1	**Ribociclib + fulvestrant (N=13)**	**n**	**13**	**13**	**13**
		Mean (SD)	12100 (5190)	1030 (401)	
		CV% mean	43.0	38.9	
		Geo-mean	11200	967	
		CV% geo-mean	42.8	37.6	
		Median	11200	997	3.83
		[Min; Max]	[5710; 23000]	[591; 1990]	[1.92; 4.28]
Cycle 1 Day 21	**Ribociclib + fulvestrant (N=13)**	**n**	**10**	**10**	**10**
		Mean (SD)	30500 (14600)	2030 (833)	
		CV% mean	48.0	41.1	
		Geo-mean	26200	1840	
		CV% geo-mean	72.7	51.1	
		Median	31800	2140	3.69
		[Min; Max]	[6120; 55200]	[803; 3390]	[1.83; 8.67]

SD: standard deviation, CV: coefficient of variation

n: number of patients with non-missing values.

CV% = coefficient of variation (%) = SD/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Source: Listing 16.2.5-3.2a

Population pharmacokinetic analysis

Method

Modeling was performed using NONMEM 7.3 and the Markov Chain Monte Carlo (MCMC) Bayesian estimation method on log-transformed PK data. The previously developed population pharmacokinetic model was used in the population modeling process. It was planned that PopPK parameters previously estimated will serve as informative priors for the PopPK analysis. Instead, for those parameters that were in the previous PopPK model, the previous estimates were used as weakly informative priors (with 50% CV) because they were based on data from studies X1101, X2101, and X2107, which were included in this analysis. The use of estimates as weakly informative priors minimized “double-counting” of the data from those 3 studies. For the parameters that were newly incorporated and represented covariate effects, non-informative priors were assumed.

The objectives of the population pharmacokinetic modeling were to: update evaluation of covariate effects on ribociclib pharmacokinetics, update evaluation of covariate effects on the ANC exposure-response relationship associated with ribociclib treatment, generate individual post-hoc longitudinal Ctrough of ribociclib to enable exposure-efficacy analyses.

The data included in the population PK analysis were from studies included in the original application (X1101, X2101, X2107, A2301) and from the studies E2301 and F2301. The design and PK sampling schedules for the first 4 studies are presented in Table 7. The design and PK sampling from studies E2301 and F2301 are presented in (

Table 8). The PopPK analysis dataset for covariate evaluation included 7960 PK observations from 1059 subjects; a breakdown of the statistics by study is listed in Table 9.

The distribution of intrinsic factors and combination partners in popPK analysis dataset are presented in Table 10 and Table 11.

Patients that received placebo were not included in the popPK analysis set. Percentage of PK measurements that were below limit of quantification in study E2301 and F2301 were 1.7% and 0.8%, respectively.

Table 7. Summary of studies from the original NCE/MAA (X1101, X2101, X2107, A2301) included in the popPK analysis

Study	Number of patients included in analysis *	Treatment regimen	PK sampling time point
X1101 Phase I study of ribociclib in Japanese patients with advanced solid tumors	N = 17	QD, 3 weeks on/1 week off Dose = 400 (N = 4) or 600 mg (N = 13)	Cycle 1 Day 1 (C1D1): 0, 0.5, 1, 2, 4, 6, 8, 24 h C1D8: 0, 1, 2, 4 h C1D15: 0, 1, 2, 4 h C1D21: 0, 0.5, 1, 2, 4, 6, 8, 24, 48, 72 h C2D1: 0 h C2D8: 2 h And unscheduled if necessary
X2101 Open label, dose-escalation Phase I study of ribociclib in patients with advanced solid tumors or lymphomas.	N = 144	QD, 3 weeks on/1 week off, or continuous Dose: 50 (N=4), 70 (N=2), 140 (N=4), 260 (N=4), 280 (N=4), 300 (N=6), 350 (N=5), 400 (N=11), 600 (N=74), 750 (N=14), 900 (N=13), or 1200 (N=3)	Non-continuous dosing: C1D1: 0, 0.5, 1, 2, 4, 6, 8, 24 h C1D8: 0, 1, 2, 4 h C1D15: 0, 1, 2, 4 h C1D21: 0, 0.5, 1, 2, 4, 6, 8, 24, 48, 72 h C2D1: 0 h C2D8: 2 h And unscheduled if necessary Continuous dosing: Same as above up to 24h on C1D21, followed by C2D1: 0, 2 h C3D1: 0, 2 h And unscheduled if necessary
X2107 (Arm 1 only: LEE011 + letrozole) Phase Ib study of the combination of ribociclib and BYL719 with letrozole in adult patients with advanced ER+ breast cancer.	N = 47	QD, 3 weeks on/1 week off Dose = 600 mg + letrozole (2.5 mg)	C1D1: 0, 0.5, 1, 2, 4, 8, 24 h C1D8: 0 h C1D15: 0 h C1D 21: 0, 0.5, 1, 2, 4, 8, 24h C2D15: 0 h C3D15: 0 h C4D15: 0 h C5D15: 0 h C6D15: 0 h And unscheduled if necessary
A2301 Randomized double-blind, placebo-controlled Phase III study of ribociclib in combination with letrozole for the treatment of postmenopausal women with HR+, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.	N = 93	QD, 3 weeks on/1 week off Dose = 600 mg LEE011+letrozole (2.5 mg)	C1D15: 0, 2 h And unscheduled if necessary

Table 8. Summary of studies with new PK data included in the popPK analysis

Study	Sample size	Ribociclib regimen	Combination therapy	PK sampling time points[g]	Endpoints
E2301 Phase III,	Total patients: N[a]=672	600 mg QD, 3 weeks on /1 week off Ribociclib/placebo: 600	Tamoxifen[f]	For a subset of ~60 subjects: * C1D15: 0, 2 h; * C3D15: 0, 1, 2, 4, 6, 8,	**Primary:** PFS (Investigator assessment) using RECIST

placebo-controlled, randomized, double-blind study/Safety, efficacy, and PK. Pre-menopausal or perimenopausal women with advanced metastatic or recurrent HR+, HER2- negative breast cancer	Ribociclib 600 mg[b]: 335	mg once daily on Days 1-21 of each 28 day cycle Tamoxifen: 20 mg daily[c]or Letrozole: 2.5 mg daily[c] or Anastrozole: 1 mg daily[c] Goserelin: 3.6 mg by subcutaneous implant on Day 1 of every 28-		24 h; * Unscheduled For the rest of subjects: * C3D15: 0, 2 h; * Unscheduled	version 1.1; Supportive Analysis: PFS (BIRC) **Key secondary:** OS **Other secondary:** ORR as defined by RECIST 1.1; CBR; TTR; DoR; ECOG performance status; Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30; Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30.
			Letrozole[f]	For a subset of ~60 subjects: * C1D15: 0, 2 h; * C3D15: 0, 2, 4, 6 h; * Unscheduled For the rest of subjects: * C3D15: 0, 2 h; * Unscheduled	
			Anastrozole[f]	For a subset of ~60 subjects: * C1D15: 0, 2 h; * C3D15: 0, 2, 4, 6 h; * Unscheduled For the rest of subjects: *C3D15: 0, 2 h; *Unscheduled	
F2301 Phase III randomized doubleblind, placebo-controlled study of ribociclib in combination with fulvestrant/Safety, efficacy, and PK. Men and postmenopausal patients with advanced metastatic or recurrent HR+, HER2-negative breast cancer	Total patients: N[a]: 727 Ribociclib 600 mg[d]: 484	600 mg QD, 3 weeks on /1 week off Ribociclib/placebo: 600 mg once daily on Days 1-21 of a 28-day cycle Fulvestrant: 500 mg (two 5 mL intramuscular injections) dosed every 28 days on the first day of each cycle with an additional dose on Day 15 of Cycle 1	Fulvestrant	For a subset of ~150 subjects: * C1D15: 0, 2, 4, 6 h; * C2D1: 0 h; * C2D15: 0, 2, 4, 6 h; * Unscheduled For the rest of subjects: * C1D15: 0 h; * C2D1: 0 h; * C2D15: 0 h; * Unscheduled	**Primary:** PFS (Investigator assessment) Supportive analysis: PFS (BIRC) **Secondary:** OS **Other secondary:** ORR and CBR per RECIST 1.1, TTR, DoR, Time to deterioration of ECOG PS, PROs (EORTC QLQ-C30, EQ-5D-5L and BPISF questionnaires) **Exploratory:** PFS2 (PFS after next line of treatment)

[a]N=number of patients who were randomized to either ribociclib arm or placebo arm
[b]Ribociclib+letrozole 2.5 mg+goserelin 3.6 mg or Ribociclib+anastrozole 1 mg+goserelin 3.6 mg or Ribociclib+tamoxifen 20 mg +goserelin 3.6 mg
[c]All days of every cycle without interruption
[d]Ribociclib+fulvestrant 500 mg
[e]N=number of subjects who received the study drug ribociclib
[f]All subjects were also receiving goserelin. Drug-drug interaction between ribociclib and goserelin is not expected as goserelin is metabolized by hydrolysis of C-terminal amino acids.
[g] CxDy represents Cycle x Day y of the treatment course.

BIRC Blinded Independent Review Committee, BPI-SF Brief Pain Inventory – Short form, CBR Clinical benefit rate, DoR Duration of response, ECOG PS Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30,EQ-5D-5L EuroQol five-dimension five-level questionnaire, ORR Overall response rate, OS Overall survival, PFS Progression-free survival, PRO Patient-reported outcomes, RECIST Response Evaluation Criteria In Solid Tumors, TTR Time to response

Table 9. Number subjects and number of observations from each study in the PopPK analysis dataset

Study	Number of subjects	Number of observations
X1101	17	407
X2101	144	3713
X2107	47	611
A2301	93	177
E2301	286	1087
F2301	472	1965
Total	1059	7960

Source script: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/create.poppk.cov.eval.dataset.main.script.R

Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/export/number.of.subj.obs.by.study.csv

Table 10. The distribution of intrinsic factors in popPK analysis dataset

Covariate	Category	N
BW#	<50kg	73
	50-60kg	205
	60-70kg	283
	70-80kg	234
	80-90kg	130
	>=90kg	130
Age	<30y	11
	30-40y	91
	40-50y	220
	50-60y	269
	60-70y	280
	>=70y	188
eGFR#	Severe (<30 mL/min/1.73m^2)	0
	Moderate (30-60 mL/min/1.73m^2)	113
	Mild (60-90 mL/min/1.73m^2)	488
	Normal (>=90 mL/min/1.73m^2)	438
Race*	Caucasian	776
	Asian	162
	Others/unknown	121

#: Subjects with missing records of the relevant covariate were excluded from the summary.
*: Race by categorization 2 (Japanese, non-Japanese Asian, all others) is not presented as this categorization was not supported by the source demographic information.
Source script:
vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/create.poppk.cov.eval.dataset.main.script.R
Source files: N.by.age.bw.egfr.csv, N.by.race.csv, with the path
vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/export/.

Table 11. The distribution of combination partners in popPK analysis dataset

Endocrine therapy	N
None	162
Anastrozole	31
Letrozole	319
Tamoxifen	75
Fulvestrant	472

Source script:
vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/create.poppk.cov.eval.dataset.main.script.R
Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/export/N.by.endocr.therapy.use.csv

Table 12: Distribution of the use of CYP3A4 inhibitors in the analysis dataset

Categorization by DI	No concurrent use	Weak inhibitors	Moderate inhibitors
No (DI = 0)	892	0	0
Yes (DI = 1)	0	94	18
In-between (0 < DI < 1)	0	36	19*

DI: dose intensity; see Section 4.4.1.2.3 for definition. The combination of DI and inhibitor class yielded 5 categories for evaluation: no concurrent use (reference), yes/weak, yes/moderate, in-between/weak, and in-between/moderate. Use of strong CYP3A4 inhibitors was not permitted per study protocols.
*: one subject in the in-between/strong category was lumped into the in-between/moderate.
Source script:
vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/create.poppk.cov.eval.dataset.main.script.R
Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.dataprep/export/N.by.cyp.inh.use.class.csv

The structural PK model and covariate investigation:

Ribociclib population PK was described using a two compartmental PopPK model with delayed zero-order oral absorption and linear clearance from the central compartment. Dose of ribociclib was recognized as a structural covariate to account for nonlinearity of ribociclib PK (on CL, Q and V2) in the original analysis and was retained in the model.

The effect of pre-specified covariates (Table 13) were investigated using the full covariate model approach, where all pre-specified covariates are added simultaneously and subsequently removed based on pre-defined criteria. The final model was employed for simulations.

The use of weak inhibitors was previously found to be statistically insignificant and clinically not important (with N=22) (PopPK Report for original MAA); in the preliminary analysis with inclusion of E2301 (before F2301 data becoming available), the effect of the yes/weak category was confirmed to be statistically insignificant and clinically not important. Hence, the use of CYP3A4 inhibitors was excluded from evaluation.

Table 13. Pre-specified popPK covariates for evaluation

Covariate	Reference state	PK parameter	Model description	Coding of covariate
			Intrinsic	
Race#	Caucasian (categorization 1)	CL	PV = PVref * $\theta_1^{I_1}$* $\theta_2^{I_2}$	I_1 = 0 & I_2 = 0, Caucasian; I_1 = 1 & I_2 = 0, Asian; I_1 = 0 & I_2 = 1, all others
	All others (categorization 2)	CL	PV = PVref * $\theta_1^{I_1}$* $\theta_2^{I_2}$	I_1 = 0 & I_2 = 0, all others; I_1 = 1 & I_2 = 0, Japanese; I_1 = 0 & I_2 = 1, non-Japanese Asian
Age	60 years old*	CL	PV = Pvref * (Age/60)^θ	-
eGFR‡	90 mL/min/1.73m²*	CL	PV = Pvref * (eGFR/90)^θ	-
			Extrinsic	
Combination partners				
Anastrozole, letrozole, tamoxifen, fulvestrant#	No combination partner	CL	PV = PVref * $\theta_1^{I_1}$ * $\theta_2^{I_2}$ * $\theta_3^{I_3}$ * $\theta_4^{I_4}$	All I's = 0, no combination partners; I_1 = 1, with anastrozole; I_2 = 1, with letrozole; I_3 = 1, with tamoxifen; I_4 = 1, with fulvestrant;
Co-medication				
CYP3A4 inhibitors#	No CYP3A4 inhibitors	CL	PV = PVref * $\theta_1^{I_1}$* $\theta_2^{I_2}$* $\theta_3^{I_3}$* $\theta_4^{I_4}$	I_1 = I_2 = I_3 = I_4 = 0, none; I_1 = 1, yes/weak; I_2 = 1, yes/moderate; I_3 = 1, in-between/weak; I_4 = 1, in-between/moderate;

#: See Section 4.4.1.2 for categorization of these covariates.

‡: Imputation for eGFR due to missing records of race followed the same approaches in the previous analysis (PopPK Report for original NDA/MAA). Briefly, Approach 1 assumed that the subjects with missing records were non-black and Approach 2 assumed that those subjects were black. Evaluation of eGFR effect was not affected by the choice of imputation approach in the previous analysis, and was confirmed in this analysis. Results from Approach 1 are presented in this report.

*: These reference values were used in previous PopPK analysis (PopPK Report for original NDA/MAA) and adopted in current analyses. They represented the medians of the population in the previous model development dataset, and were close to the medians in current dataset (57 years old and 84.9 mL/min/1.73m²).

CL: apparent clearance

PV: parameter value

Results

The trace plots indicate MCMC convergence of the full model. The point estimates of the Gelman-Rubin statistic (PSRF) were close to 1 and the upper 95% confidence boundaries did not exceed 1.05 which indicates that satisfactory MCMC Bayesian convergence was reached.

The popPK full covariate model included all the covariates except CYP3A4 inhibitors and race by categorization 2. The 95% CIs of the covariate effects of eGFR, Race Asian, Race Others, letrozole, and fulvestrant were entirely within the ±20% reference ranges, suggesting that these effects were not clinically important. For age, the 95% CI extended slightly out of the reference ranges, suggesting it was not clinically

important. For anastrozole on CL/F, there was 25% probability for its effect to be greater than the reference range (mean 1.127 (0.936 - 1.353 (95%CI))). The wide CI indicates that there is insufficient information to estimate the effect. The distributions of simulated effects of BW on CL, Q, and V2 shrank relative to those in the previous analysis. As such, the effect of BW on CL became clinically not important. Among all the covariates, BW on Q and V2 (BW_Q, BW_V2) and tamoxifen on CL appeared to be important. Tamoxifen was estimated to increase ribociclib apparent clearance by 36.4% (95% CI: 19.9% - 54.3%) (based on parameter posterior associated with tamoxifen effect in Figure 4. VPC for final popPK model (at 600 mg steady state)

Table 14). This effect translates to a decrease in the overall exposure of ribociclib by 26.7% (95% CI: 16.6% - 35.2%) with concurrent use of tamoxifen.

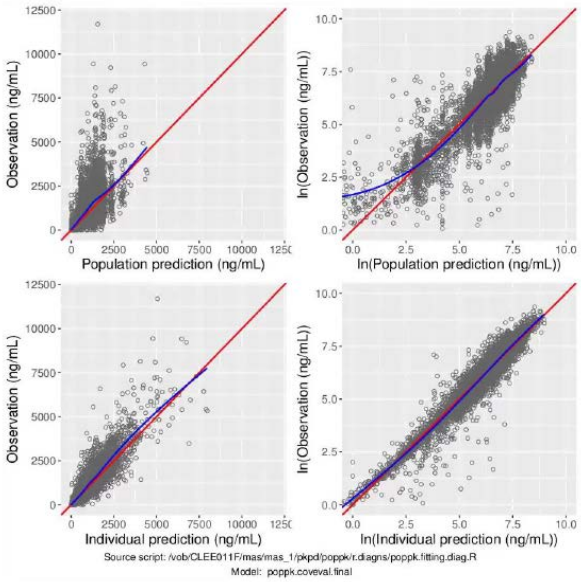
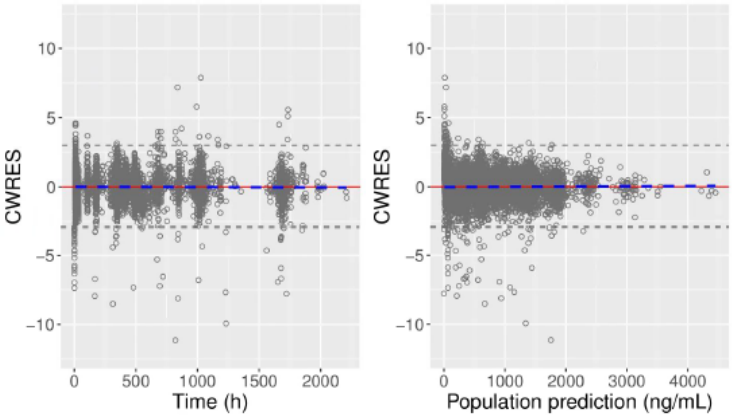


Figure 1. Observations vs. population and individual predictions by popPK final model



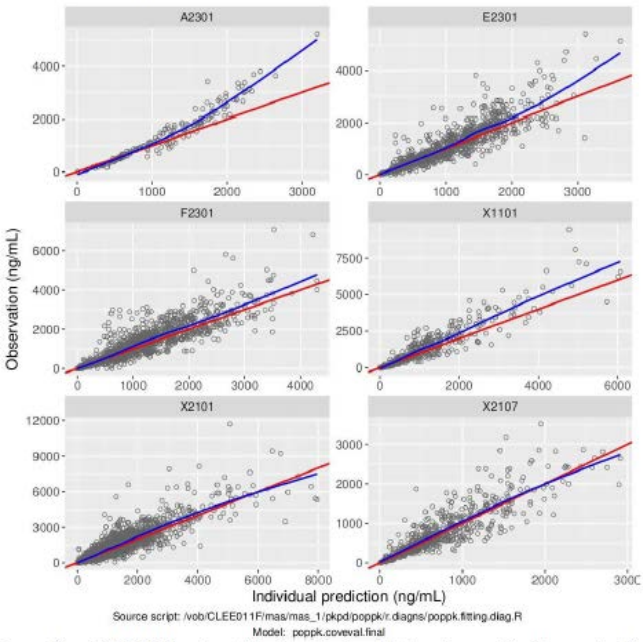
Source script: /vob/CLEE011F/mas/mas_1/pkpd/poppk/r.diagns/poppk.fitting.diag.R
Model: poppk.coveval.final

Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.diagns/plots/poppk.coveval.final/residual.based.diagns.pdf.

Note: The cone-shaped distribution in the CWRES vs. population prediction does not indicate deficiency in the residual model; rather, it was driven by the data from study X2101 where the number of data points tapers with increase in exposure (see Figure 9-4).

Symbols: individual CWRES; red line: zero line; blue broken line: linear regression line; gray broken lines indicate CWRES=±3.

Figure 2. CWRES vs. time and population predictions by popPK final model

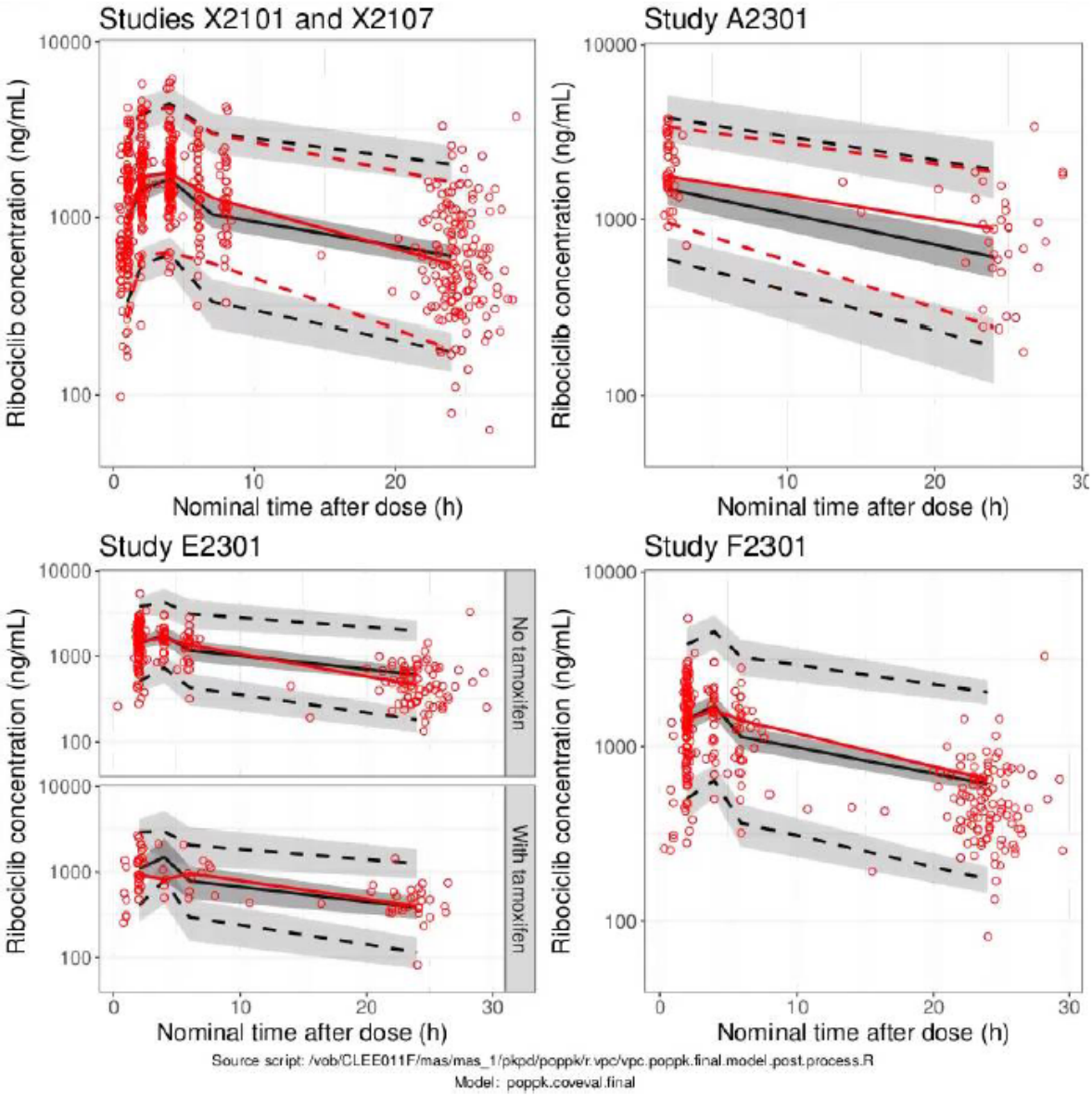


Source script: /vob/CLEE011F/mas/mas_1/pkpd/poppk/r.diagns/poppk.fitting.diag.R
Model: poppk.coveval.final

Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.diagns/plots/poppk.coveval.final/dv.vs.preds.pdf.

Note: Symbols: individual data points; red line: unity line; blue line: smoothing line.

Figure 3. Study stratified observations vs. individual predictions by PopPK final model



Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/vpc/plots/conc.profile.vpc.all.one.page.pdf

Note: Red circles: observed data; red solid and broken lines: median and 5th or 95th percentile of observed data; black solid and broken lines: means of the median and 5th or 95th percentile of model simulations; gray areas indicate 90% confidence intervals of the above means. For statistical summarization, data and simulated values were binned by nominal time points 1, 2, 4, 7, and 24 h in studies X2101 and X2107, 2 and 24 h in study A2301, and 2, 4, 6, and 24 h in studies E2301 and F2301 after previous dose.

Figure 4. VPC for final popPK model (at 600 mg steady state)

Table 14. PopPK final model parameter posteriors

Parameter	Mean‡	SD‡	Naive SE‡	Time-series SE‡	Effective N‡	95% CI‡	Null value*
D1 (h)	3.4	Fixed	NA	NA	NA	NA	NA
V1 (L)	249.827	11.443	0.054	0.238	2329	(228.034 - 272.549)	NA
CL (L/h)	26.761	0.484	0.002	0.01	2289	(25.828 - 27.723)	NA
Q (L/h)	73.465	3.893	0.018	0.149	680	(65.961 - 81.351)	NA
V2 (L)	839.908	23.001	0.108	0.668	1199	(794.101 - 885.565)	NA
ALAG1 (h)	0.403	0.002	0	0	3648	(0.398 - 0.407)	NA
Dose_CL (-)	-0.404	0.049	0	0.002	573	(-0.503 - -0.313)	0
Dose_Q (-)	-0.59	0.085	0	0.002	1789	(-0.757 - -0.426)	0
Dose_V2 (-)	-0.438	0.06	0	0.002	920	(-0.557 - -0.323)	0
BW_Q (-)	0.834	0.175	0.001	0.004	2146	(0.482 - 1.171)	0
BW_V2 (-)	0.316	0.079	0	0.002	1431	(0.161 - 0.472)	0
Tamoxifen_CL (-)	1.409	0.082	0	0.002	1354	(1.251 - 1.572)	1
ω^2_{V1}	0.729	0.063	0	0.001	3406	(0.616 - 0.861)	NA
ω^2_{CL}	0.238	0.013	0	0	8032	(0.213 - 0.266)	NA
ω^2_{CL-Q}	0.109	0.021	0	0.001	1386	(0.068 - 0.152)	NA
ω^2_{Q}	0.263	0.05	0	0.002	585	(0.176 - 0.373)	NA
ω^2_{CL-V2}	0.199	0.016	0	0	2948	(0.168 - 0.231)	NA
ω^2_{Q-V2}	0.186	0.029	0	0.001	1079	(0.134 - 0.246)	NA
ω^2_{V2}	0.251	0.024	0	0.001	1954	(0.208 - 0.3)	NA
$\sigma^2_{additive}$ in log domain	0.207	0.004	0	0	12807	(0.2 - 0.215)	NA
MCMCOBJ	-7200.39	300.736	1.418	13.735	479	(-7827.086 - -6650.075)	NA

Model run number: poppk.coveval.final.

‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 10000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

Parameter	Mean‡	SD‡	Naive SE‡	Time-series SE‡	Effective N‡	95% CI‡	Null value*

*: null values: reference values indicating that there are no covariate effects;

All parameters in the form of covariate_PK parameter are parameters representing covariate effects; the dashes in parentheses indicate the related parameters are unitless.

Source script: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.diagns/poppk.bayes.convg.diag.R

Source file: vob/CLEE011F/mas/mas_1/pkpd/poppk/r.diagns/export/poppk.coveval.final/parameter.posteriors.summary.csv

Special populations

The PopPK dataset included subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m2, N=438), mild impairment (60 ≤ eGFR<90 mL/min/1.73m2, N=488), and moderate impairment (30 ≤ eGFR<60 mL/min/1.73m2, N=113). Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation. eGFR was investigated as a continuous covariate on ribociclib CL/F. The eGFR effect on ribociclib CL/F was estimated to have a 95% CI of 0.894, 1.080 (mean=0.991), indicating no clinical importance of renal function on ribociclib PK for patients with mild and moderate renal impairment.

Pharmacokinetic interaction studies

Results of drug-drug interaction studies were assessed in the original MAA submission and are described in the approved SmPC.

Co-administration with NSAI, goserelin and fulvestrant

In the present application, each combination partner was investigated as a covariate in the population PK model on ribociclib apparent clearance (see further above). All subjects receiving NSAI were also receiving goserelin (see discussion on clinical pharmacology).

2.3.3. Pharmacodynamics

No new clinical studies were submitted in support of this application (see discussion on clinical pharmacology).

2.3.4. PK/PD modelling

The MAH provided the following data in support of this application:

- Characterization of the relationship between ribociclib exposure and clinical efficacy endpoints as measured by progression free survival (PFS) and time to response (TTR) based on data from Studies E2301, F2301, and A2301.

- Further characterization of the relationship between ribociclib exposure and clinical safety endpoints based on data in Study E2301, Study F2301, and data included in the original MAA: QTc prolongation as measured by the QTcF change from Baseline, focusing on the impact of combination partners on the ribociclib PK-QTc relationship; Neutropenia as measured by newly occurring post Baseline grade 3 or worse neutropenia; Longitudinal absolute neutrophil count (ANC), based on previously developed population ANC exposure-response (E-R) model included in the original MAA, with a focus on covariate effects.

Table 15: Pooling strategy for exposure-response analyses

Purpose of analysis	Population	Studies
Exposure-efficacy	Advanced breast cancer with HR+, HER2-, 3 weeks on/1 week off regimen	A2301, E2301[a], and F2301[b]
PK-QT	Solid tumor[c]	Original NDA package[d], E2301, and F2301
Exposure-neutropenia	Solid tumor, 3 weeks on/1 week off regimen	Original NDA package[d], E2301[a], and F2301

[a]Patients from E2301 who were assigned to tamoxifen (in the treatment assignment case report form) were excluded from the exposure-efficacy and exposure-neutropenia pool.
[b]Only patients from F2301 with no prior endocrine therapy for advanced disease were included in the exposure-efficacy pool.
[c]PK-QT analysis data set included both 3 weeks on/1 week off regimen and continuous regimen. Visits after C1D22 pre-dose of continuous dosing patients were not included.
[d]Original NDA package includes studies X1101, X2101, X2107 (ribociclib+letrozole patients), and A2301.

The Safety set included all patients who received at least one dose of ribociclib.

The PK-Safety set included all A2301, and E2301 patients who were not assigned to tamoxifen (in the treatment assignment case report form), and F2301 patients with no prior endocrine therapy for advanced disease in safety set, and who had at least one population PK model predicted ribociclib Ctrough.

The PK-Neutropenia set included all patients in the safety set who were not assigned to tamoxifen (in the treatment assignment case report form), and had at least one evaluable steady state trough ribociclib concentration (denoted as SS Ctrough) and non-missing Baseline neutrophil count of grade 0, 1, or 2. For patients with a newly occurring grade 3 or worse neutropenia post Baseline (defined as Baseline grade is lower than grade 3, i.e., the Baseline grade is either grade 0, 1 or 2, and post Baseline value is grade 3 or higher), at least one evaluable steady-state concentration is required on or before the day of the newly occurring grade 3 or worse neutropenia to be included in the PK-Neutropenia set.

The PK-ECG set included all patients in the Safety set with non-missing Baseline ECG (electrocardiogram) and at least one time-matched PK-ECG assessment.

Demographic and Baseline characteristics of patients in each analysis set are presented in Table 16.

Table 16. Demographics and Baseline characteristics (Safety set)

Demographic variable	Safety set N=1367	PK-Safety set N=672	PK-ECG set N=997	PK-Neutropenia set N=573
Age (years)				
n	1367	672	997	573
Mean (SD)	57.1 (12.73)	56.1 (12.92)	56.5 (12.64)	58.4 (12.22)
Median	58.0	56.0	57.0	59.0
Min-Max	22-91	25-89	22-89	25-85
Age category-n (%)				
<40 years	123 (9.0)	75 (11.2)	99 (9.9)	38 (6.6)
40 - <65 years	799 (58.4)	396 (58.9)	596 (59.8)	333 (58.1)
≥ 65 years	445 (32.6)	201 (29.9)	302 (30.3)	202 (35.3)
Sex-n (%)				
Female	1292 (94.5)	672 (100.0)	923 (92.6)	526 (91.8)
Male	75 (5.5)	0	74 (7.4)	47 (8.2)
Race-n (%)				
Non-Asian	1173 (85.8)	557 (82.9)	844 (84.7)	477 (83.2)
Asian	194 (14.2)	115 (17.1)	153 (15.3)	96 (16.8)
Weight (kg)				
n	1360	669	993	570
Mean (SD)	70.46 (16.003)	70.06 (15.649)	70.50 (15.960)	71.09 (15.824)
Median	68.10	68.00	68.60	69.00
Min-Max	34.2-158.8	35.3-130.0	34.2-158.8	39.4-130.0
ECOG performance status-n (%)				
0	850 (62.2)	444 (66.1)	622 (62.4)	356 (62.1)
1	514 (37.6)	226 (33.6)	372 (37.3)	217 (37.9)
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
Missing	3 (0.2)	2 (0.3)	3 (0.3)	0

Source: Appendix 2-Table 3-1.1

Exposure-efficacy

Progression-free survival and time-to-response

Exposure-efficacy analyses using pooled data from Study A2301, Study E2301, and Study F2301 were conducted to explore the relationship between ribociclib exposure and efficacy endpoints. Geometric mean population PK model predicted ribociclib Ctrough on non-zero dosing days serves as an overall measure of exposure; in the presence of dose reductions and interruptions, time-varying ribociclib DI up to the event (efficacy event or censoring) and time-varying mean population PK model predicted Ctrough up to the event (efficacy event or censoring) were planned in order to account for the change in exposure over time (Table 17).

Table 17. Exposure-efficacy analyses

Efficacy endpoints	Exposure variables	Methods
PFS, TTR	(1) Time-varying ribociclib DI up to the event	Extended Cox model, Time-varying boxplot
	(2) Time-varying mean population PK model predicted ribociclib Ctrough[a] up to the event	Extended Cox model, Time-varying boxplot
PFS,TTR	Geometric mean population PK model predicted ribociclib Ctrough[a] on non-zero dosing days	Cox model, KM plot

DI: Dose intensity; PFS: progression free survival; TTR: Time to response (CR or PR)
[a]For a given patient ribociclib Croughs were predicted from the Population PK model

The results from the extended Cox model for PFS/TTR vs. time-varying mean population PK model predicted Ctrough and time-varying dose intensity (DI) up to the event is presented in Table 18 and Table 19.

Table 18. Extended Cox regression model of PFS with time-varying mean model predicted Ctrough or DI up to the event (PK-Safety set)

Prognostic variables	Hazard ratio	95% CI	p-value
Ctrough (ng/mL)	0.98[a]	(0.93, 1.03)	0.465
Dose intensity (mg/day)	0.98[b]	(0.97, 0.99)	<0.001

[a]Hazard ratio is given for a 100*ng/mL change in Ctrough.
[b]Hazard ratio is given for a 10*mg/day change in dose intensity.
Source: Appendix 1-Table 3-1.4 and Appendix 1-Table 3-1.6

Table 19. Extended Cox regression model of TTR with time-varying mean model predicted Ctrough or DI up to the event (PK-Safety set)

Prognostic variables	Hazard ratio	95% CI	p-value
Ctrough (ng/mL)	1.06[a]	(1.01, 1.11)	0.019
Dose intensity (mg/day)	1.03[b]	(1.02, 1.04)	<0.001

[a]Hazard ratio is given for a 100*ng/mL change in Ctrough.
[b]Hazard ratio is given for a 10*mg/day change in dose intensity.
Source: Appendix 1-Table 3-1.5 and Appendix 1-Table 3-1.7

The figures below show PFS and TTR by quartiles of geometric mean model predicted Ctrough based on Kaplan Meier estimates..

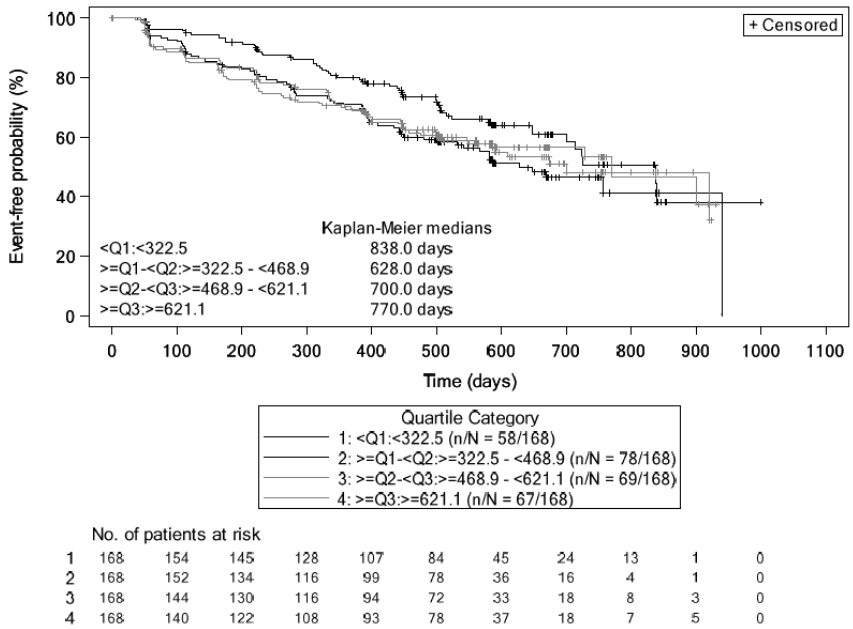


Figure 5. Kaplan-Meier plot of PFS by quartiles of geometric mean model predicted Ctrough (ng/mL) on non-zero dosing days (PK-Safety set)

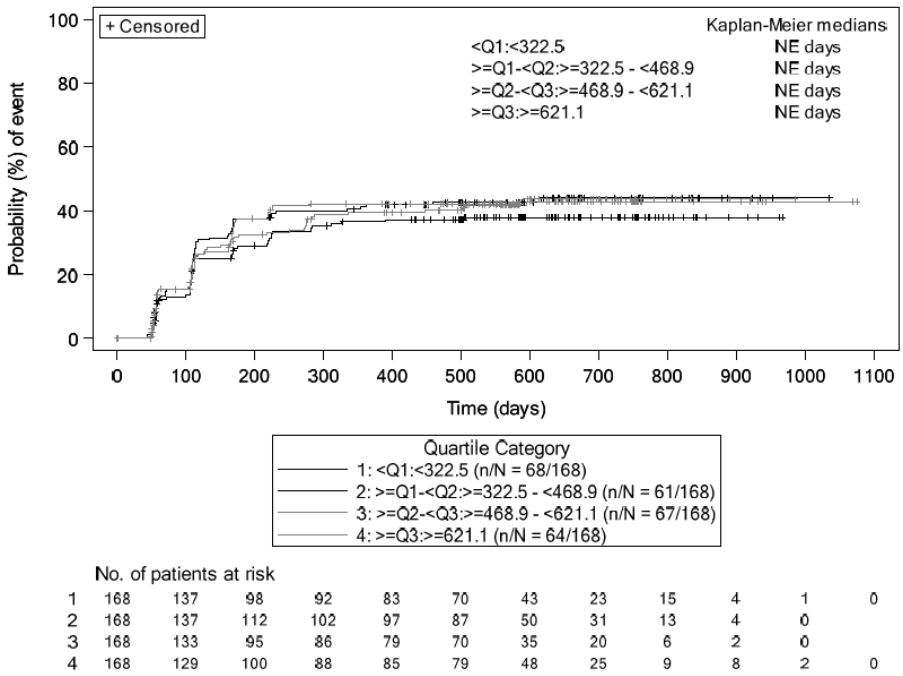


Figure 6. Kaplan-Meier plot of TTR by quartiles of geometric mean model predicted Ctrough (ng/mL) on non-zero dosing days (PK-Safety set)

Exposure-safety analysis

The planned exposure-safety analyses using pooled data are summarized in Table 20.

Table 20. Planned exposure-safety analyses

Safety endpoints	Analysis by exposure endpoints	Methods
QTcF change from Baseline	QTcF change from Baseline vs. matched ribociclib PK concentration. Statistical_methods	Linear mixed model
Newly occurring post Baseline grade 3 or worse neutropenia (Yes/No)	Summary of occurrence of new grade 3 or worse neutropenia by geometric mean steady state ribociclib Ctrough up to the event.	Boxplot
Absolute neutrophil count (ANC)	Longitudinal ANC vs. population PK model predicted individual PK time course	Nonlinear mixed effect model

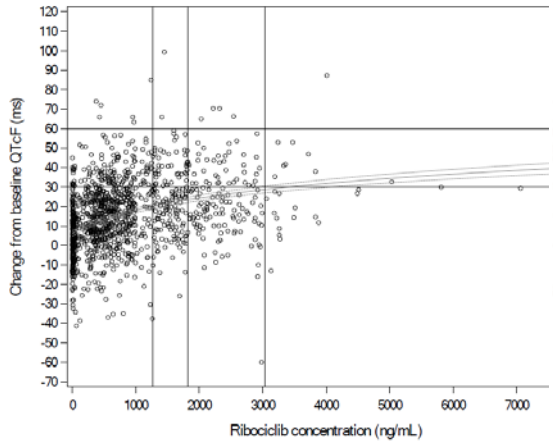
Effect of ribociclib with combination partner on cardiac electrophysiology

The relationship between ribociclib exposure and QT interval prolongation in cancer patients was characterized using a linear mixed model of the log transformed concentration (as in the original MAA). The model was fitted using SAS.

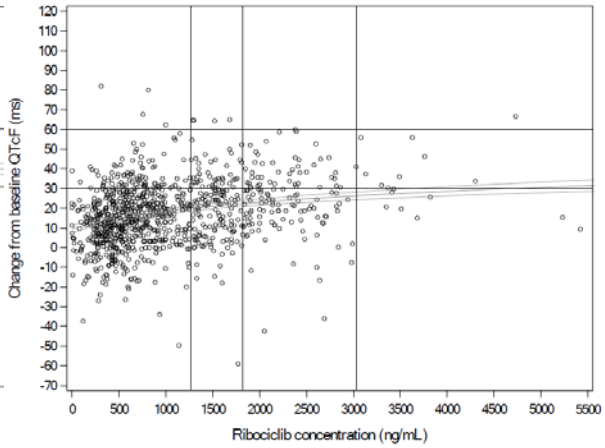
QTc prolongation was observed with increase in ribociclib concentration in patients with cancer in Study E2301 and Study F2301. PK-QTc analysis showed that combination partner was a significant covariate.

Figure 7. Scatter plot and 90% CI of QTcF change from baseline versus ribociclib concentration PK-ECG set Median concentration = 709 ng/mL, median baseline QTcF = 414.3 ms.

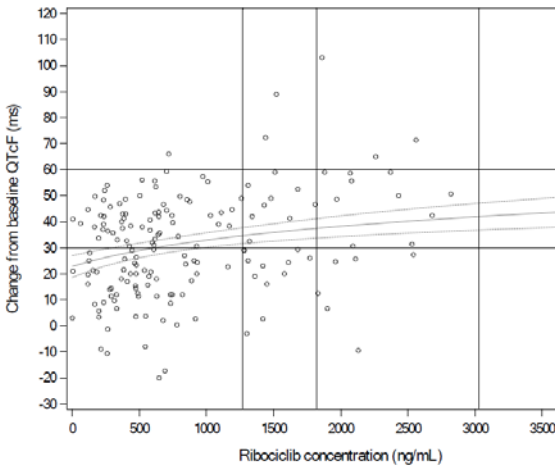
A. Combination Partner = Fulvestrant



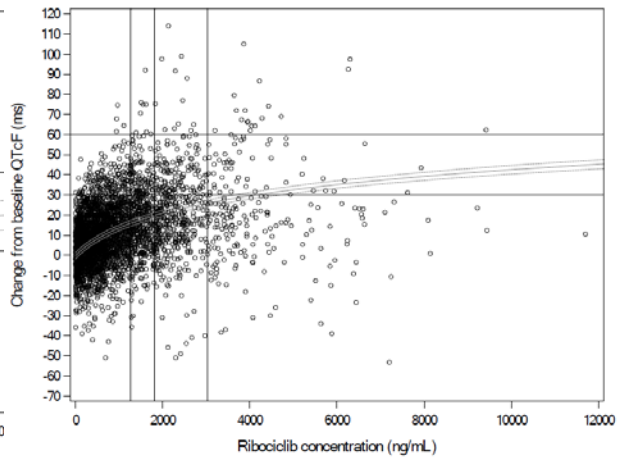
B. Combination Partner = NSAI (letrozole or anastrozole)



C. Combination Partner = Tamoxifen



D. Combination Partner = No combination



The plots (A-D) shows a linear mixed model with subject as a random effect, and mean function in the form of Delta QTcF = log(concentration/median concentration + 1) + (baseline QTcF – median baseline QTcF) + combination + combination* log(concentration/median concentration + 1). Vertical lines from left to right are Q1, median, and Q3 of ribociclib Cmax on C1D18/C1D21 from 600 mg patients in X2101. Horizontal dotted lines are the reference lines at 30 ms and 60 ms.

Using the geometric mean steady-state Cmax of ribociclib as a single agent from Study X2101, the estimated mean ΔQTcF at the ribociclib 400 mg dose was lower compared to the estimates at ribociclib 600 mg in the same combination partner group (Table 21).

Table 21. Estimated mean QTcF change from baseline from QTcF-ribociclib concentration model (PK-ECG set)

Concentration level	Concentration (ng/mL)	Baseline QTcF (ms)	Estimated mean QTcF change from baseline (ms) (90% CI)
Combination partner = Tamoxifen			
400 mg Cmax single regimen*		410.0	
Geo mean	1040		33.2 (30.40, 36.04)
Q1	730		30.9 (28.28, 33.61)
Median	1230		34.4 (31.38, 37.40)
Q3	1570		36.3 (32.83, 39.67)
600 mg Cmax single regimen*		410.0	
Geo mean	1880		37.7 (33.89, 41.52)
Q1	1270		34.6 (31.57, 37.68)
Median	1820		37.5 (33.71, 41.20)
Q3	3030		42.0 (36.78, 47.15)
600 mg Cmax combo**		410.0	
Geo mean	1290		34.7 (31.64, 37.78)
Q1	863		32.0 (29.27, 34.67)
Median	1200		34.2 (31.24, 37.18)
Q3	1890		37.8 (33.94, 41.60)
Combination partner = NSAI (letrozole or anastrozole)			
400 mg Cmax single regimen*		415.0	
Geo mean	1040		18.7 (17.46, 19.91)
Q1	730		16.7 (15.47, 17.94)
Median	1230		19.7 (18.44, 20.97)
Q3	1570		21.3 (19.95, 22.71)
600 mg Cmax single regimen*		415.0	
Geo mean	1880		22.6 (21.09, 24.10)
Q1	1270		19.9 (18.64, 21.18)
Median	1820		22.4 (20.90, 23.86)
Q3	3030		26.3 (24.31, 28.31)
600 mg Cmax combo**		415.0	
Geo mean	1730		22.0 (20.56, 23.44)
Q1	1500		21.0 (19.65, 22.34)
Median	1670		21.8 (20.35, 23.18)
Q3	2150		23.6 (21.99, 25.24)
Combination partner = Fulvestrant			
400 mg Cmax single regimen*		415.0	
Geo mean	1040		18.4 (17.28, 19.51)
Q1	730		15.7 (14.67, 16.78)
Median	1230		19.8 (18.61, 20.95)
Q3	1570		22.0 (20.70, 23.26)

Concentration level	Concentration (ng/mL)	Baseline QTcF (ms)	Estimated mean QTcF change from baseline (ms) (90% CI)
600 mg Cmax single regimen*		415.0	
Geo mean	1880		23.7 (22.31, 25.08)
Q1	1270		20.1 (18.88, 21.24)
Median	1820		23.4 (22.03, 24.76)
Q3	3030		28.7 (26.96, 30.47)
Combination partner = No combination			
400 mg Cmax single regimen*		410.7	
Geo mean	1040		14.0 (12.61, 15.40)
Q1	730		10.9 (9.51, 12.30)
Median	1230		15.6 (14.20, 17.01)
Q3	1570		18.1 (16.72, 19.58)
600 mg Cmax single regimen*		410.7	
Geo mean	1880		20.1 (18.67, 21.59)
Q1	1270		15.9 (14.52, 17.33)
Median	1820		19.8 (18.33, 21.24)
Q3	3030		25.9 (24.36, 27.52)

*Based on C1D18/C1D21 Cmax from Study X2101
**Based on C3D15 Cmax from E2301 with the respective combination partner using the study level Pharmacokinetic Analysis Set.
Baseline QTcF is the median baseline of patients in PK-ECG set with the respective combination of covariates in the model.
The model is a linear mixed model with patient as a random effect, and mean function in the form of Delta QTcF = log(concentration/median concentration + 1) + (baseline QTcF -median baseline QTcF) + combination + combination* log(concentration/median concentration + 1).

Exposure – Neutropenia relationship

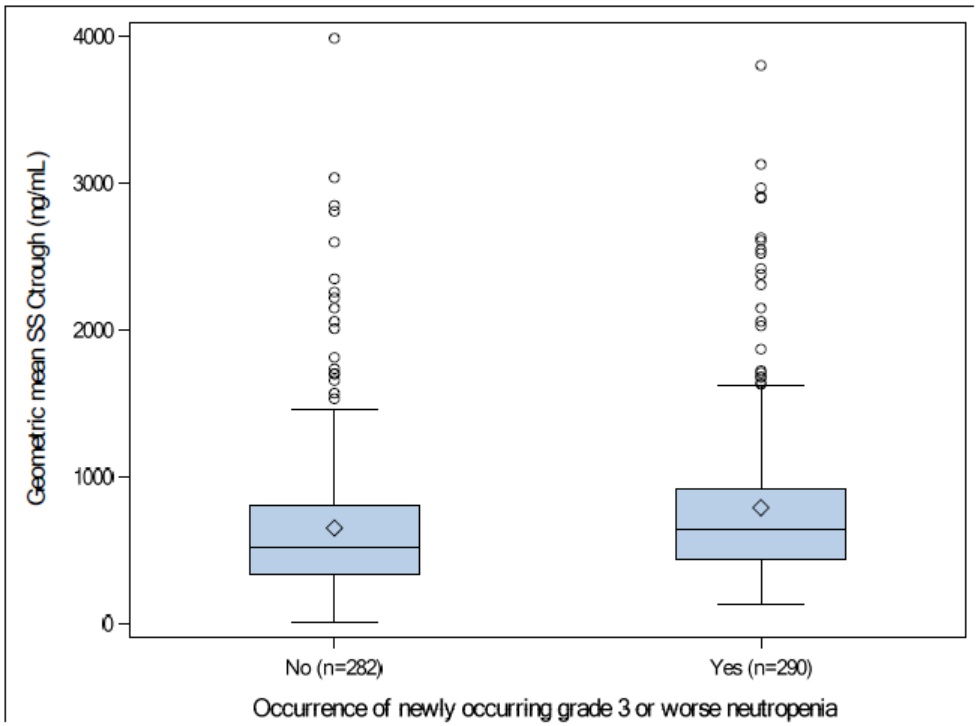
While the exposure (geometric mean steady state Ctrough up to the event) was overlapping in patients with or without grade 3 or worse neutropenia, generally higher exposure was observed for those with a grade 3 or worse event, indicating an association between ribociclib exposure and occurrence of grade 3 or worse neutropenia (Table 22, Figure 8).

Table 22. Geometric mean steady state (SS) ribociclib Ctrough (ng/mL) up to the event by occurrence of newly occurring grade 3 or worse neutropenia (PK-Neutropenia set)

Parameter	Statistics	Occurrence = Yes N = 290	Occurrence = No N = 283
Geometric mean SS Ctrough (ng/mL)	n	290	282
	Mean (SD)	789 (564)	651 (538)
	CV%	71.5	82.6
	Geo-mean	649	476
	Geo-CV%	67.2	110.2
	Median	636	519
	Min-Max	133-3800	4.48-3990

n = number of patients with corresponding geometric mean SS ribociclib
SD: Standard deviation; CV = Coefficient of variation
Source: Appendix 2-Table 3-3.1

Figure 8. Boxplot of geometric mean SS ribociclib Ctrough (ng/mL) up to the event by occurrence of newly occurring grade 3 or worse neutropenia (PK-Neutropenia set)



Diamonds represent the mean and circles represent values outside of 1.5*IQR.Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.
Source: Appendix 2-Figure 3-3.1

Effect of ribociclib with combination partner on neutropenia (absolute neutropenia count (ANC))

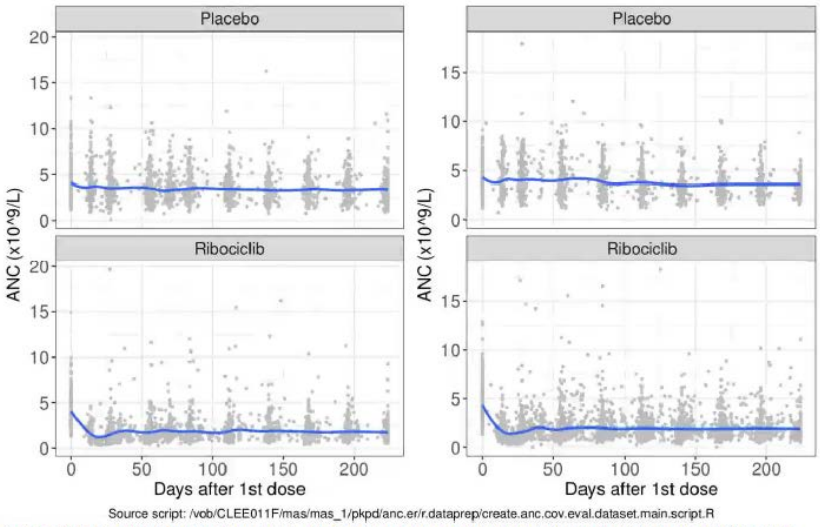
Exposure-response (E-R) analyses of absolute neutropenia count (ANC) were conducted. The longitudinal E-R relationship for neutropenia was characterized using a log-linear drug effect model coupled with a semi-mechanistic model for describing clinical ANC kinetic data after anticancer drug treatment. Cancer type and use of letrozole were in the original MAA application retained as covariates on the slope (a parameter representing potency) of ribociclib effect. No further model development was deemed necessary and with the addition of E2301 and F2301 data, the ANC E-R model was utilized to update the evaluation of effects of covariates (Table 23).

The analysis dataset for covariate evaluation included 7786 ANC data points from 1052 subjects. Study E2301 contributed 27.0% of the subjects and 29.1% of the observations, respectively; study F2301 contributed 44.7% of the subjects and 38.5% of the observations, respectively.

In the current analysis, simultaneous incorporation of all prespecified covariates into the previously established final model (PopPK Report for original NCE/MAA) caused failure in achieving MCMC convergence. A stepwise procedure was employed to enable MCMC convergence and two versions of stable full model (anc.coveval.full6 and anc.coveval.full7) were reached (differing by one covariate, fulvestrant vs. letrozole (on Base and Slope).

Statistical significance was detected for the associations between ECOG status and tumor type ($p=1.82\times10^{-9}$), between ECOG status and use of combination partner ($p=5.94\times10^{-13}$), and between tumor type and use of combination partner ($p<2.2\times10^{-16}$). These findings were used to inform covariate removal, if necessary, from a full covariate model to ensure model stability.

Figure 9. ANC profiles in the first 8 cycles in studies E2301 (left) and F2301 (right)



Source script: /vob/CLEE011F/mas/mas_1/pkpd/anc.er/r.dataprep/create.anc.cov.eval.dataset.main.script.R

Source file: vob/CLEE011F/mas/mas_1/pkpd/anc.er/r.dataprep/plots/lee011e.f2301.anc.vs.time.pdf

Note: Gray symbols represent individual observations and blue curves are loess smoothing.

Table 23. Pre-specified ANC E-R covariates for evaluation

Covariate	Reference state	Related E-R parameters	Model description	Coding of covariate
			Intrinsic	
Race	Caucasian	Base, Slope	PV = PVref * $\theta_1^{I_1}$* $\theta_2^{I_2}$	I_1 = 0 & I_2 = 0, Caucasian; I_1 = 1 & I_2 = 0, Asian; I_1 = 0 & I_2 = 1, all others
Age	60 years old*	Base, Slope	PV = Pvref * (Age/60)^θ	-
			Extrinsic	
Combination partners				
Anastrozole, letrozole, tamoxifen, fulvestrant	No combination partner	Base, Slope	PV = PVref * $\theta_1^{I_1}$ * $\theta_2^{I_2}$ * $\theta_3^{I_3}$ * $\theta_4^{I_4}$	All I's = 0, no combination partners; I_1 = 1, with anastrozole; I_2 = 1, with letrozole; I_3 = 1, with tamoxifen; I_4 = 1, with fulvestrant;

*: The reference value was used in previous PopPK analysis (PopPK Report for original NDA/MAA) and adopted in current analyses. It represented the median of the population included in the previous model development dataset, and was close to the median in current dataset (57 years old).

Base: a parameter in the E-R model that represented the baseline ANC prior to treatment.

Slope: a parameter in the E-R model that represented the potency of ribociclib for inhibiting proliferation/differentiation of progenitor cells.

Incorporation of covariates to the Base was primarily for satisfactory description of ANC observations prior to treatment. The covariate-Slope relations were the focus for evaluation and interpretation of covariate effects on the potency of ribociclib for lowering ANC.

PV: parameter value

ref: reference value of a parameter

θ: a fixed-effect parameter to be estimated

I: category indicator of a covariate

Two versions of stable full model were reached, and from these two versions of the final model were derived. The two final models differed by the covariates on Base; anc.final1 retained the RaceAsian-Base relation, and anc.final2 retained letrozole-Base and tamoxifen-Base relations. No covariates were retained on the Slope in either model.

Only results from one model were presented (anc.final1). The final model achieved MCMC convergence as suggested by the trace plots and the Gelman-Rubin test results (point estimates were close to 1 and the upper confidence boundaries did not exceed 1.05).

The combination partners were either found to have any statistically significant or clinically relevant effect on the ANC E-R relationship. Race of Asian, and concomitant use of letrozole or tamoxifen were significant covariates on baseline ANC. The base in Asian subjects was 10.1% (95% CI, 3.7% - 16.1%) lower than in non-Asian subjects. The base in subjects using letrozole was 15.3% (95% CI, 10.1% - 20.2%) lower, and in subjects using tamoxifen 10.9% (95% CI, 1.0% - 19.7%) lower. The effects of all other covariates on Base and Slope were considered negligible.

The parameter posteriors are presented in Table 24.

Table 24. Parameter posteriors from ANC E-R final model (anc.final1)

Parameter	Mean‡	SD‡	Naive SE‡	Time-series SE‡	Effective N‡	95% CI‡	Null value*
ANCbase (x10^9/L)	4.1166	0.0576	0.0004	0.0019	952	(4.0055 - 4.2311)	NA
Slope (1/log(ng/mL))	0.0254	0.0005	0	0	153	(0.0243 - 0.0264)	NA
MTT (h)	118.7426	1.7826	0.0133	0.1212	222	(115.2961 - 122.105)	NA
Gamma (-)	0.1828	0.0044	0	0.0003	175	(0.1739 - 0.1915)	NA
RaceAsian_Base (-)	0.8541	0.0254	0.0002	0.0012	475	(0.8046 - 0.9027)	1
ω^2_{Base}	0.0974	0.0065	0	0.0002	1464	(0.0852 - 0.1105)	NA
$\omega^2_{Base\sim Slope}$	-0.0069	0.0034	0	0.0001	637	(-0.0135 - 1e-04)	NA
ω^2_{Slope}	0.0179	0.003	0	0.0001	410	(0.0126 - 0.0243)	NA
$\sigma^2_{additive}$ in log domain	0.1161	0.0021	0	0	8750	(0.1121 - 0.1203)	NA
MCMCOBJ	-13607.5	187.9928	1.4011	10.0123	359	(-13995.4576 - -13253.2553)	NA

‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 10000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

*: null values: reference values indicating that there are no covariate effects;

All parameters in the form of covariate_parameter are parameters representing covariate effects; random effects and residual error expressed as variance.

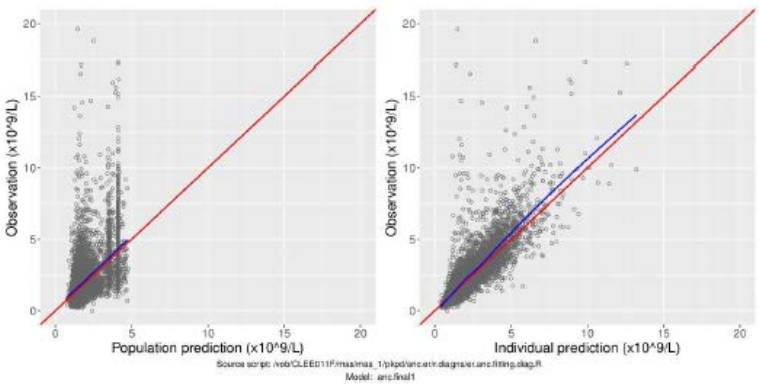
The dashes in parentheses indicate the related parameters are unitless.

Source script: vob/CLEE011F/mas/mas_1/pkpd/anc.er/r.diagns/er.anc.bayes.convg.diag.R

Source file: vob/CLEE011F/mas/mas_1/pkpd/anc.er/r.diagns/export/anc.final1/parameters.summary.csv

The DV vs. PRED and DV vs. IPRED plots demonstrate agreement between observations and population as well as individual predictions from the model (Figure 10, Figure 12). No apparent deficiency in the structural or residual model was identified in the residual-based diagnostic plots (Figure 11).

Figure 10. Observations vs. population and individual predictions by ANC E-R final model (anc.final1)



Source file: vob/CLEE011F/mas/mas_1/pkpd/anc.er/r.diagns/plots/anc.final1/dv.vs.preds.pdf.

Note: Symbols: individual data points; red line: unity line; blue line: smoothing line.

Figure 11. CWRES vs. time and population predictions by ANC E-R final model (anc.final1)

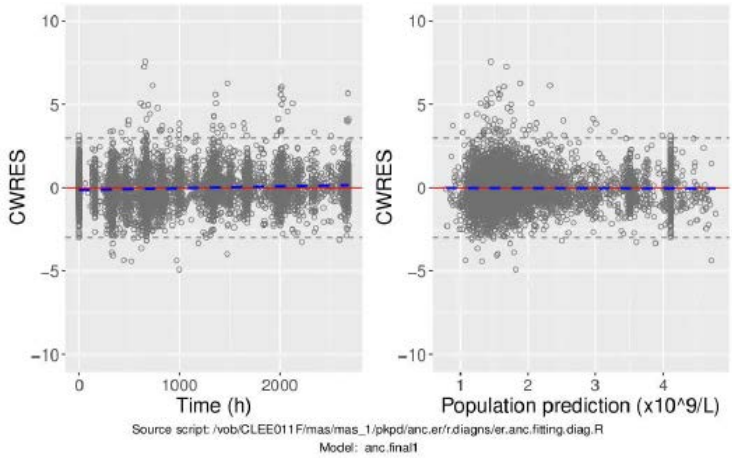
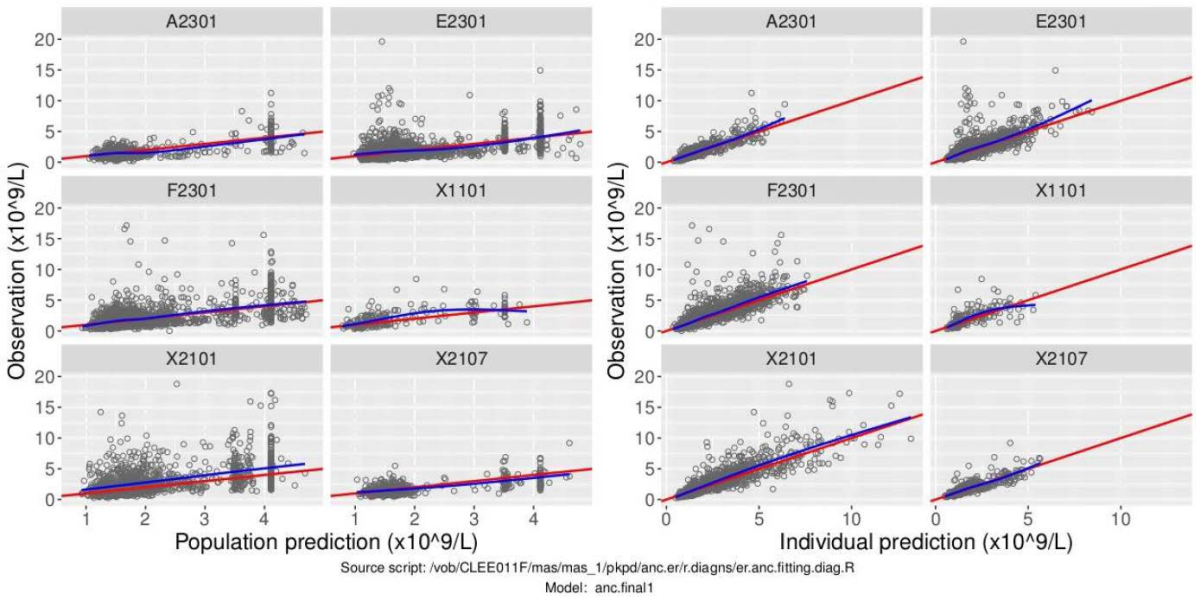


Figure 12. Study-stratified observations vs. population and individual predictions by ANC E-R final model



Source file: vob/CLEE011F/mas/mas_1/pkpd/anc.er/r.diagns/plots/anc.final1/dv.vs.preds.pdf.
Note: Symbols: individual data points; red line: unity line; blue line: smoothing line.

2.3.5. Discussion on clinical pharmacology

The two studies (E2301 and F2301) were designed to investigate the interaction, efficacy and safety of ribociclib treatment in combination with the following active substances: letrozole, anastrozole and tamoxifen (all three co-administered with goserelin) and fulvestrant. Dense and sparse PK samples were collected for assessment of the interaction between the combinations ribociclib, letrozole, anastrozole and tamoxifen.

The impact of ribociclib on letrozole, anastrozole and tamoxifen was assessed with non-compartmental analysis. Cmax, Cthrough and AUC of ribociclib, tamoxifen, letrozole and anastrozole exposure parameters at Cycle 3 Day 15 were compared.

Ribociclib exposures were slightly lower in combination with tamoxifen and tamoxifen exposure increased approximately 2-fold. Due to safety reasons in relation to QTcF prolongation, this combination is not proposed by the applicant (see below). For the combination of 600 mg ribociclib and letrozole, letrozole PK data suggested no apparent interaction. Due to small number of patients with evaluable PK parameters of ribociclib in combination with anastrozole (n=3), a conclusion cannot be drawn. However, data from study E2301 indicated no clinically relevant drug interaction between ribociclib and anastrozole following co administration.

The LEQ803 concentration (metabolite of ribociclib) was largely comparable among the combination partners suggesting no marked impact on LEQ803 exposure. No comparison with historical LEQ803 data was done (ribociclib administered without combination partner). The PK of fulvestrant was not evaluated in study F2301. Therefore a possible impact of ribociclib on fulvestrant PK has not been fully evaluated. However, mechanistically and based on the knowledge on fulvestrant, it is deemed unlikely that ribociclib (a moderate to strong CYP3A4 inhibitor) has a clinically relevant impact on fulvestrant PK. There are no known DDI with fulvestrant. *In vitro* studies showed no relevant inhibition by fulvestrant for major CYP enzymes. Interaction studies with rifampicin (strong CYP3A4 inducer) and ketoconazole (strong CYP3A4 inhibitor) demonstrated no effect on fulvestrant PK.

Concomitant consumption of grapefruit or grapefruit juice, both of which are known to inhibit CYP3A enzymes, may increase the exposure of ribociclib. Concomitant consumption of pomegranate was not prohibited in studies A2301, E2301 and F2301. Although, *in vitro* experiments showed that pomegranate juice inhibited CYP3A, the MAH provided three papers on the *in vivo* interaction of pomegranate and midazolam and simvastatin (Farkas et al 2007, Misaka et al 2011, Park et al 2016). These clinical studies revealed that consumption of pomegranate juice did not modify the activity of CYP3A in humans. Therefore, it is unlikely that co administration of pomegranate or pomegranate juice would have any clinically meaningful increase in ribociclib exposure and the proposal to delete the recommendation to avoid pomegranates or pomegranate juice in the SmPC section 4.5 is acceptable.

A population PK approach was conducted to characterize the pharmacokinetics of ribociclib. The popPK model was conducted to evaluate potential interactions between ribociclib and combination partner, as well as for investigation of the impact of intrinsic factors. Additionally, the model was used for predictions of Cthrough in the exposure-response analysis.

The dataset included the new studies as well as data from 4 previously conducted studies (ribociclib alone or in combination with letrozole). A previously developed two-compartment model with delayed zero-order oral absorption and linear clearance from the central compartment described the ribociclib PK, with dose and body weight recognized as covariates on CL, Q and V2.

The objectives of the popPK modeling were to re-evaluate and update the covariate effects on ribociclib pharmacokinetics. The covariates investigated were bodyweight, age, eGFR, race (Asian or others) and combination partner (letrozole, anastrozole, tamoxifen and fulvestrant). The covariates retained in the final model were dose on CL, Q and V2, body weight on Q and V2 and tamoxifen on CL.

For ribociclib and tamoxifen combination, ribociclib exposure (AUC) was estimated to be reduced by 26.7% (95% CI: 16.6, 35.2) in combination with 20 mg tamoxifen based on population PK analysis, and tamoxifen exposure was approximately 2-fold higher when administered with 600 mg ribociclib as compared to placebo in Study E2301. However, the changes in ribociclib and tamoxifen exposure were not considered to be clinically relevant as patients who were dose reduced from the starting dose of 600 mg to lower doses had a PFS benefit and dose reduction had no impact on the response. This combination is not proposed in this

application due to a safety issue in relation to QTcF prolongation (see further below and SmPC sections 4.4 and 4.5).

All subjects receiving NSAI were also receiving goserelin. However drug-drug interaction between ribociclib and goserelin is not expected as goserelin is metabolized by hydrolysis of C-terminal amino acids.

The analysis did not indicate a relevant impact of letrozole or fulvestrant on ribociclib PK. There is insufficient information on the combination of ribociclib and anastrozole (n=31). Anastrozole as a covariate on ribociclib CL/F was found to have a 25% probability of being >20% from the reference value. However, this effect was deemed to be minor and the evaluation was limited by sample size (N=31 with the use of anastrozole, accounting for only 2.9% of the population in the analysis dataset).

The handling of covariates in the covariate analysis had flaws. With the full covariate approach, whenever there is a correlation coefficient of >0.3 between two covariates, these should be handled with caution. This was not adhered to for e.g. eGFR and age on CL, therefore the possible impact of renal function on ribociclib PK has not been properly investigated in this analysis. However, with regard to the impact of eGFR, the applicant has conducted a dedicated study in patients with renal impairment which is under assessment (EMEA/H/C/4213/II/03/G).

The goodness-of-fit plots of the final population PK model showed some deviation from the normal scatter around the identity lines in the observed versus predicted concentration plots. The prediction corrected VPCs that were provided showed an acceptable prediction of the observed median concentration over time, however, an over prediction of the 95th percentile and under prediction of the 5th percentile were observed. There appeared to be an under prediction of the concentration over time in study X1101 (Japanese patients) however, the individual values fell within the range of all observed concentrations. The available pharmacokinetic data do not warrant an adjustment due to race.

No additional drug-drug interactions studies were provided. Section 4.5 of the SmPC has been updated to reflect available data on interactions between ribociclib and anastrozole, fulvestrant or tamoxifen respectively. It has also been updated to reflect that drug-drug interaction studies between ribociclib and oral contraceptives have not been conducted.

Exposure-efficacy analyses were conducted to explore the relationship between ribociclib Ctrough,avg,ss and efficacy endpoints PFS and TTR. In the presence of dose reductions and interruptions, time-varying ribociclib dose intensity and mean population PK model predicted Ctrough up to the event (efficacy event or censoring) were planned. A significant relation between PFS and TTR and dose intensity (DI) was estimated using an extended cox proportional hazards regression model. This relationship is not considered to be clinically relevant. The cox regression analysis using Ctrough suggest a lack of relationship. Although dose modifications are reflected in DI variable, it is still not independent since modifications are based on pharmacodynamic response. In conclusion, no clear relationship was found between ribociclib exposure metrics and the efficacy endpoints.

QT prolongation is an important identified safety risk for ribociclib. The ECG data showed a slightly higher frequency of notable QTcF values in Study E2301 and F2301 compared to Study A2301, which could be explained by the differences in ECG collection methodology and time points between these studies. The majority of post baseline ECG assessments collected in Study E2301 and F2301 were single measurements (approximately 80% and 75% respectively) thereby potentially subject to greater variations than average of triplicate measurements, and an additional mid-cycle measurement was performed on C3D15 in Study E2301 and C2D15 in Study F2301.

Updated PK-QTcF analysis showed that the combination partner was a significant covariate. Using the PK-QTcF model, at the geometric mean steady-state Cmax of the ribociclib 600 mg dose with NSAI (letrozole or anastrozole) as combination partner from Study E2301, the estimated mean ΔQTcF was 22.0 ms (90% CI: 20.56, 23.44). Using the geometric mean steady-state Cmax of the ribociclib 600 mg as a single agent

from Study X2101, the estimated mean ΔQTcF with fulvestrant as combination partner was 23.7 ms (90% CI: 22.31, 25.08). The model-estimated mean ΔQTcF values with the combination partners were consistent with the observed data. In combination with an aromatase inhibitor, QTcF events of > 480 ms are reversible and managed with dose modifications. Ribociclib in combination with tamoxifen showed that a higher frequency of notable QTcF and ΔQTcF values were observed in patients receiving tamoxifen compared to letrozole and anastrozole (estimated mean ΔQTcF at the geometric mean steady-state Cmax of ribociclib 600 mg 34.7 ms (90% CI: 31.64, 37.78)). The mean ΔQTcF was consistently higher (> 10 ms) in the placebo plus tamoxifen subgroup than in the placebo plus NSAI subgroup, suggesting tamoxifen alone has a QT prolongation effect. Based on an imbalance in increased QTcF values and higher ΔQTcF observed in the ribociclib plus tamoxifen subgroup, the MAH has decided not to include the ribociclib and tamoxifen combination in the proposed indication. Section 4.4 of the SmPC reflects the results of study E2301 (MONALEESA-7) in which a QTcF interval increase >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a non steroidal aromatase inhibitor (NSAI). Kisqali is not recommended to be used in combination with tamoxifen (see section on clinical safety and SmPC sections 4.4 and 4.5).

Due to the risk of QT prolongation when used in combination, the SmPC was modified to recommend restarting Kisqali at the next lower dose level after resolution of the first occurrence of QTcF >480 ms versus resuming at the same dose level (as currently stated in the Kisqali label) (see SmPC section 4.2). Furthermore, it is considered that one ECG showing QTcF greater than 500 msec is sufficient to interrupt Kisqali hence the mention of at least 2 separate was deleted from the SmPC section 4.2. Section 4.5 of the SmPC has also been updated to add ciprofloxacin, levofloxacin, azithromycin to the list of medicinal products that are known to prolong the QT interval and should be avoided in combination with Kisqali.

The results of the exposure – neutropenia analyse indicated a slight association between ribociclib exposure and occurrence of grade 3 or worse neutropenia, which is in line with the results presented in the original MAA.
The longitudinal E-R relationship for neutropenia was characterized using a log-linear drug effect model coupled with a semi-mechanistic model for describing clinical ANC kinetic data. The factors, including age, race, and combination partners (letrozole, anastrozole, tamoxifen, fulvestrant), were evaluated for their effects on the ANC E-R relationship of ribociclib, on the parameters of Base (baseline ANC) and Slope (ribociclib potency for inhibition of progenitor cell proliferation). None of the covariates were found to have clinically important effect on Slope based on the simulated covariate effect sizes and the relevant predefined criteria, indicating that the ANC E-R relationship of ribociclib was not affected by age, race, or the use of letrozole, anastrozole, tamoxifen, or fulvestrant. Race of Asian, and concomitant use of letrozole or tamoxifen were significant covariates on baseline ANC. Only race of Asian was retained in the model, letrozole was not considered to be clinically relevant. A VPC of the ANC versus time was provided and indicated the model captured the general trend in the observed data although a slight over prediction of the median was observed.

2.3.6. Conclusions on clinical pharmacology

The PK of ribociclib has been previously described and the PK and PD data presented in this submission is generally in line with previous results.

Overall, data from study E2301, a clinical study in patients with breast cancer, indicated no clinically relevant drug interaction between ribociclib and anastrozole following co administration of these medicinal products. Furthermore no clinically relevant effects of fulvestrant on ribociclib exposure following co administration of these medicinal products were reported in study F2301.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

See discussion on clinical efficacy.

2.4.2. Main studies

Study E2301 – MONALEESA-7

A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer.

Methods

Study participants

Key inclusion criteria
- Adult female patients , aged ≥18 and < 60 - Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or patient had a hysterectomy. - Pre- or peri-menopausal status; premenopausal defined as either: i) last menstrual period within the last 12 months. ii) if on tamoxifen or toremifene within the past 14 days, plasma estradiol, and follicle stimulating hormone (FSH) was to be in the premenopausal range per local normal range. iii) in case of therapy induced amenorrhea, plasma estradiol and/or FSH was to be in the premenopausal range per local normal range. Patients who had bilateral oophorectomy were not eligible Peri-menopausal status was defined as neither pre- nor postmenopausal (see exclusion criteria) - Patients had advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy (e.g. surgery and/or radiotherapy). - Patients who received (neo) adjuvant therapy for breast cancer were eligible: i) If the patient never received any prior endocrine therapy OR if ≥12 months had elapsed since the patient's last dose of adjuvant therapy, then the patient was eligible to receive tamoxifen plus goserelin or a NSAI plus goserelin for advanced breast cancer based on the investigator's choice. ii) If tamoxifen or fulvestrant was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient was eligible to receive a NSAI (letrozole or anastrozole) plus goserelin for advanced breast

cancer.

iii) If letrozole, anastrozole, or exemestane was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient was eligible to receive tamoxifen plus goserelin for advanced breast cancer.

- Patients who received ≤ 14 days of tamoxifen or a NSAI (letrozole or anastrozole) with or without goserelin or only goserelin ≤ 28 days for advanced breast cancer prior to randomization were allowed. Patients were to continue treatment with the same hormonal agent plus goserelin during the study. No treatment interruption was required for these patients prior to randomization.
- Patients who received up to one line of chemotherapy for advanced breast cancer and discontinued 28 days before randomization.
- Histological and/or cytological confirmation of estrogen receptor (ER)-positive and/or progesterone receptor-positive breast cancer by local laboratory.
- HER2-negative disease.
- Patients had either measurable disease, i.e. at least one measurable lesion as per Response Evaluation Criteria in Solid Tumors RECIST v1.1 criteria OR if no measurable disease was evident at least one predominantly lytic bone lesion was to be present.
- ECOG 0 or 1.
- Patient had adequate bone marrow and organ function.

Key exclusion criteria

- Prior CDK4/6 inhibitor therapy.
- Patients with known hypersensitivity to any of the excipients of ribociclib or goserelin or hormonal treatment assigned
- Patients were postmenopausal. Postmenopausal status was defined either by:

  i) Prior bilateral oophorectomy

  ii) Age ≥ 60

  iii) Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.

  iv) If taking tamoxifen or toremifene, and age < 60, then FSH and plasma estradiol level in postmenopausal ranges per local laboratory normal range.

  For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure menopausal status (NCCN breast cancer guidelines Ver. 1.2018)
- Patients with inflammatory breast cancer at Screening.
- Patients who received any prior hormonal anti-cancer therapy for advanced breast cancer, except for 14 days of tamoxifen or NSAI or goserelin ≤ 28 days for advanced breast cancer prior to randomization.
- Patients who had not had resolution of all acute toxic effects of prior anti-cancer therapy

to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

- Patients with a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated basal cell skin carcinoma, squamous cell skin carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
- CNS metastasis.
- Patients with impairment of gastrointestinal (GI) function or GI disease that significantly alter the absorption of the study drugs
- Patients with a known history of human Immunodeficiency virus infection
- Patients with any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study
- Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality.
- Patients currently receiving any of the following substances and where use could not be discontinued seven days prior to the start of the treatment: Known strong inducers or inhibitors of CYP3A4/5, Medications with a known risk to prolong the QT interval or induce Torsades de Pointes that cannot be discontinued or replaced by safe alternative medication, Medications with a narrow therapeutic window and which are predominantly metabolized through CYP3A4/5, for patients receiving tamoxifen: known strong inducers or inhibitors of CYP2D6, Herbal preparations/medications and dietary supplements (except vitamins)
- Patient who had major surgery within 14 days prior to starting study drug or had not recovered from major side effects
- Patients who were currently receiving warfarin or other Coumadin-derived anti-coagulant
- Patients who were currently receiving or those who had received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who had not fully recovered from the side effects of such treatment.
- Patients were concurrently using other antineoplastic agents (except for patients who received ≤ 14 days of tamoxifen or NSAI or goserelin ≤ 28 days for advanced breast cancer prior to randomization).
- Patients who received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who had not recovered to grade ≤ 1 from related side effects of such therapy (with the exception of alopecia) and/or if ≥ 25% of the bone marrow was irradiated.
- Pregnant or nursing (lactating) women.
- Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing of study treatment and for 21 days after stopping study medication.
- Patients with symptomatic visceral disease or any disease burden that made the patient

ineligible for endocrine therapy per the Investigator's best judgment.

Treatments

Patients were randomly assigned to one of the following treatment arms in a 1:1 ratio to either the ribociclib or placebo arm:

- Ribociclib 600 mg days 1-21 of each 28-day cycle plus tamoxifen 20 mg QD or a NSAI (letrozole 2.5 mg QD or anastrozole 1 mg QD) plus goserelin 3.6 mg subcutaneously of each 28-day cycle.
- Placebo plus tamoxifen or a NSAI (letrozole or anastrozole) plus goserelin.

Study treatment continued until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression. Switching the endocrine combination partners was also not permitted.

Objectives

Primary objective: To determine whether treatment with ribociclib plus goserelin plus either tamoxifen or a nonsteroidal aromatase inhibitor (NSAI) prolongs progression-free survival (PFS) compared to treatment with placebo plus goserelin plus either tamoxifen or a NSAI in premenopausal women with HR-positive, HER2-negative advanced breast cancer.

Key secondary objective: To determine whether treatment with ribociclib plus goserelin plus either tamoxifen or a NSAI prolongs overall survival (OS) compared to treatment with placebo plus goserelin plus either tamoxifen or a NSAI in premenopausal women with HR-positive, HER2-negative advanced breast cancer.

Other secondary objectives:

- To evaluate the safety and tolerability of ribociclib plus goserelin plus either tamoxifen or a NSAI.

- To evaluate the two treatment arms with respect to ORR and clinical benefit rate (CBR).

- To describe time to response (TTR) and duration of response (DOR) in each treatment arm.

- To evaluate the two treatment arms with respect to time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status.

- To evaluate patient-reported outcomes (PROs) for health-related quality of life (QoL) in the two treatment arms.

Exploratory objectives: To characterize the pharmacokinetics (PK) of tamoxifen/NSAI with or without co-administration with ribociclib; To characterize the PK of ribociclib when administered with goserelin plus either tamoxifen or a NSAI; To assess differences in molecular alterations (main pathways of interest in breast cancer) in patients deriving benefit from treatment; To explore molecular alterations in circulating tumor deoxyribonucleic acid (ctDNA); To explore potential mechanisms of resistance to treatment with ribociclib with goserelin plus either tamoxifen or a NSAI; To assess any effect on estradiol (E2) suppression relative to baseline with or without co-administration with ribociclib in patients treated with NSAIs; To evaluate the effect of cytochrome P450 (CYP) 2D6 genotype on tamoxifen biotransformation and/or response to tamoxifen treatment; To explore potential mechanisms of hepatotoxicity; To describe work productivity and activity impairment in the two treatment arms; To explore potential differences in hospital resource utilization; To explore the long-term benefit intermediate to PFS and OS; by measurement of PFS2.

Outcomes / endpoints

Primary endpoint: Progression free survival. The primary efficacy variable was PFS from Investigator's review of radiology data using RECIST v1.1 criteria.

Key secondary endpoint: Overall survival defined as the time from date of randomization to date of death due to any cause.

Other secondary endpoints were: ORR, clinical benefit rate (CBR), TTR, DOR, time to deterioration of ECOG status, health-related quality of life (QoL), safety and tolerability.

Overall response rate was defined as the proportion of patients with best overall response of confirmed CR or PR according to RECIST v1.1, and CBR was defined as the proportion of patients with a best overall response of confirmed CR or PR, or stable disease lasting 24 weeks or longer, according to RECIST v1.1 criteria.

Time to response (CR or PR) was defined as the time interval between date of randomization and the first documented response (CR or PR, which had to be confirmed subsequently).

Duration of response (DoR) was defined as the time from documentation of tumor response to disease progression.

ECOG performance status was used to assess physical health of patients ranging from 0 (most active) to 5 (least active). An analysis of time to definitive deterioration of the ECOG PS was performed and summarized using K-M method. The two treatment groups were compared using a stratified log-rank test at a one-sided 2.5% level of significance. Deterioration was defined as an increase in ECOG PS by at least one category from the baseline score or death due to any cause. Deterioration was considered definitive if ECOG PS had no return to baseline or better at a time subsequent to the deterioration during the treatment period.

Patient-reported outcomes (PROs) were evaluated using the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) and breast cancer specific questionnaire (EORTC QLQ-BR23, version 1.0). EuroQoL 5-level instrument (EQ-5D-5L, Version 4.0) was used to evaluate PRO measures of health-related quality-of-life (HR-QOL), functioning, disease symptoms and treatment-related side effects. In addition, the Work Productivity and Activity Impairment-General Health (WPAI-GH, version 2.0) was used to explore the impact of study treatments on work productivity/productivity loss (Reilly et al 1993).

Exploratory endpoints included: PK, molecular alterations (including ctDNA), mechanisms of resistance, estradiol (E2) suppression, effect of cytochrome P450 (CYP) 2D6 genotype on tamoxifen, work productivity and activity impairment, hospital resource utilization, mechanisms of hepatotoxicity (not analyzed at this cut-off), PFS2.

Sample size

The assumption of median PFS of 9 months in the control arm (tamoxifen/NSAI plus goserelin) for the sample size calculation was based on a meta-analysis of four studies including pre-menopausal patients advanced breast cancer. These patients were treated with a combination of tamoxifen and luteinizing hormone-releasing hormone agonist[9] and the results of a letrozole study in breast cancer patients[10]. It was expected that the addition of ribociclib would result in a 33% reduction in the hazard rate (corresponding to an increase in median PFS to 13.4 months assuming PFS had an exponential model assumption).

If the true HR was 0.67 (under the alternative hypothesis), a total of 329 PFS events would provide 95% power at a one-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank

[9] Klijn et al 2001
[10] Mouridsen et al 2001

test. Considering a recruitment period of approximately 18 months at a uniform rate of 33 patients/month, 600 patients were needed to be randomized to the two treatment arms in a 1:1 ratio. Assuming about 10% patients would be lost to follow-up for PFS, a total of 660 patients were needed be randomized. Given the above assumptions, it was estimated that the 329th PFS event would be observed approximately 22 months from the date of first patient randomized in the study.

Randomisation

Eligible patients were randomized, stratified by the presence of liver and/or lung metastases (yes versus no), prior chemotherapy for advanced disease (yes versus no), and endocrine combination partner (tamoxifen and goserelin versus NSAI and goserelin).

Blinding (masking)

This was a double-blind study.

Statistical methods

Analysis set

The Full Analysis Set (FAS) consisted of all randomized patients. Following the intent-to-treat principle, patients were analyzed according to the treatment and stratum they were assigned to at randomization. The FAS was the primary analysis set for efficacy analyses.

The Safety Set consisted of all patients who received at least one dose of any component of study treatment. Patients were analyzed according to the treatment actually received, which refers to the randomized treatment unless the alternative treatment was received throughout the study.

The Per-protocol Set (PPS) included the subset of patients from the FAS without a major protocol deviation and who took at least one dose of study treatment.

The Pharmacokinetic Analysis Set included all patients who provided at least one evaluable PK concentration.

Efficacy analyses

PFS

According to the final SAP, no interim analysis was planned for PFS. The primary endpoint PFS was to be assessed after approximately 329 (event rate 50%) events had been documented.

Assuming a median PFS of 9 months for the control arm vs. 13.4 months for the ribociclib arm (HR 0.67), the 329 events would provide 95% power to reject the null hypothesis (log-rank, one-sided, 2.5% level significance, strata based on CRF data).

OS

A hierarchical testing strategy, where OS was to be statistically evaluated only if the primary efficacy endpoint PFS was statistically significant favoring the treatment arm, was used to control the overall type-I error rate.

Up to three analyses were planned for OS. A median OS of 33 months was assumed for the control arm and 47 months for the ribociclib arm (HR 0.7).

For the OS-analyses, an α-spending function according to Lan-DeMets (O'Brien-Fleming), was used to maintain the overall type I error probability.

The cumulative conditional power to reject the null hypothesis (log-rank, one-sided, 2.5% level significance) is presented in the table below.

Table 25: Timelines for interim and final analyses - Study E2301

Months after randomization of the first patient	PFS events	Cumulative Power (%) against a hazard ratio of 0.67	OS events	Cumulative Conditional Power (%) against hazard ratio of 0.7
22	329 (100%)	95	123 (49%)	15
30	--	--	189 (75%)	54
40	--	--	252(100%)	80

Blinded independent review (BIRC) in audit sample

PFS assessed by Blinded Independent Review Committee (BIRC) was used as a supportive analysis of the primary endpoint.

Based on the audit size calculation approach proposed by Dodd et al (2011), assuming investigator and BIRC assessments are similar and the estimated log of investigator-based HR was -0.40 (i.e. HR=0.67), the audit size of 40% ensured that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio had 86% probability of being below zero (i.e. HR < 1) if the correlation between investigator assessment and BIRC assessment was 0.7 (the estimated correlation based on data from the BELLE-2 [CBKM120F2302] study in metastatic breast cancer).

The following thresholds based on the NCI[11] and PhRMA[12] methods were used to define the trigger for a full BIRC review:

- If the upper-bound of the one-sided 95% confidence interval for BIRC-based log-hazard ratio exceeded zero (i.e. HR>1) based on the NCI method

and/or

- If ≥15% differential discordance was observed in early discordance rate (EDR) or late discordance rate (LDR) according to Amit et al 2011.

[11] Dodd et al 2011
[12] Amit et al 2011

Results

Participant flow

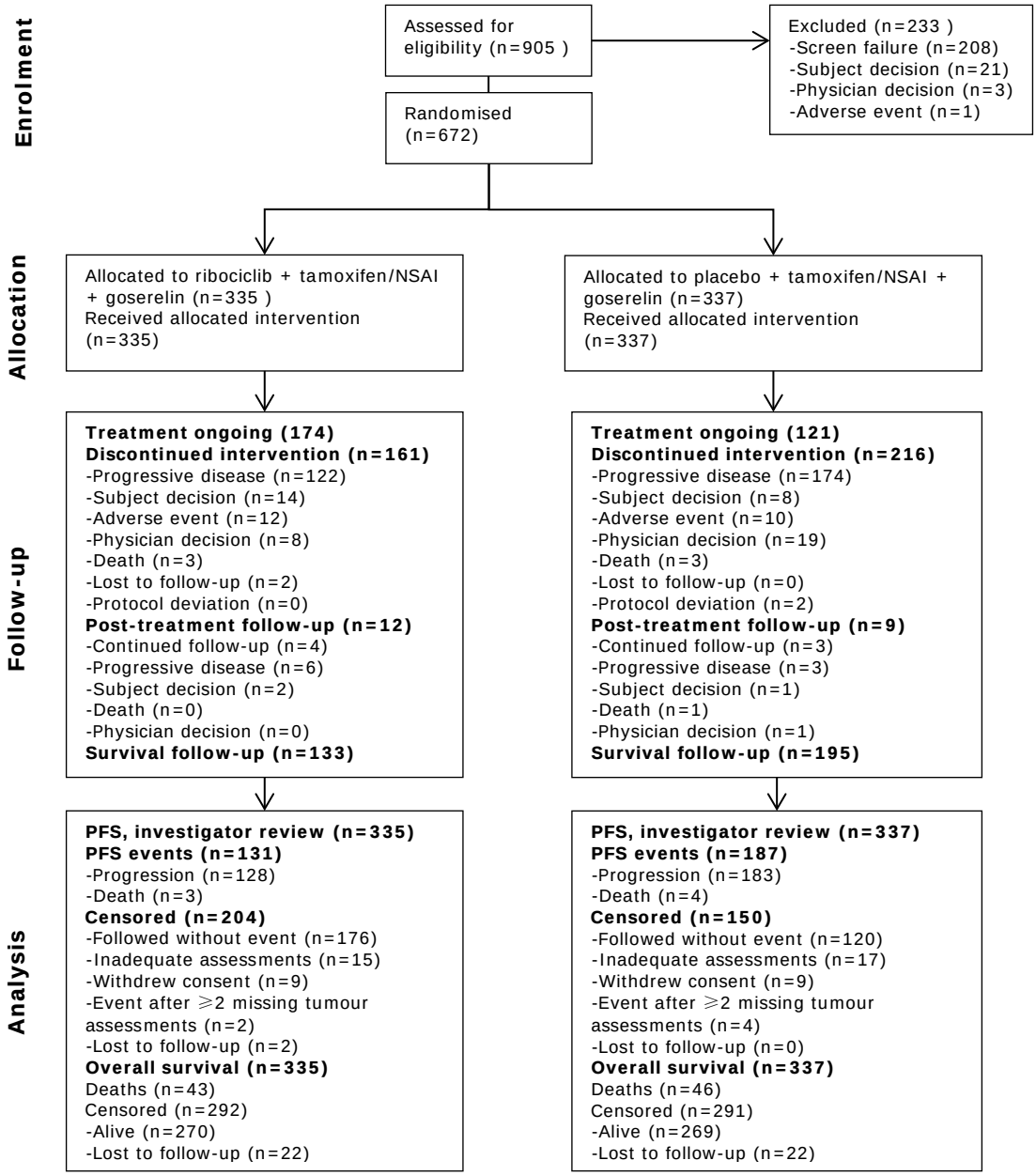


Figure 13: Participant flow - Study E2301

Table 26: Patient disposition (FAS) – Study E2301

Disposition Reason	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Patients randomized			
Treated	335 (100)	337 (100)	672 (100)
Patients treated			
Treatment ongoing[1]	174 (51.9)	121 (35.9)	295 (43.9)
End of treatment	161 (48.1)	216 (64.1)	377 (56.1)
Reason for end of treatment			
Progressive disease	122 (36.4)	174 (51.6)	296 (44.0)
Patient/guardian decision	14 (4.2)	8 (2.4)	22 (3.3)
Adverse event	12 (3.6)	10 (3.0)	22 (3.3)
Physician decision	8 (2.4)	19 (5.6)	27 (4.0)
Death	3 (0.9)	3 (0.9)	6 (0.9)
Lost to follow-up	2 (0.6)	0	2 (0.3)
Protocol deviation	0	2 (0.6)	2 (0.3)
Entered post-treatment follow-up[2]	12 (7.5)	9 (4.2)	21 (5.6)
No longer being followed in post-treatment follow-up	8 (5.0)	6 (2.8)	14 (3.7)
Continued to be followed in post-treatment follow-up	4 (2.5)	3 (1.4)	7 (1.9)
Reason for end of post-treatment follow-up[3]			
Progressive disease	6 (50.0)	3 (33.3)	9 (42.9)
Patient/guardian decision	2 (16.7)	1 (11.1)	3 (14.3)
Death	0	1 (11.1)	1 (4.8)
Physician decision	0	1 (11.1)	1 (4.8)
Entered survival follow-up[2]	133 (82.6)	195 (90.3)	328 (87.0)

[1]Patients continue study treatment at the time of the cut-off 20 AUG 2017.

Recruitment

In total, 905 patients were screened for entry into this study, of which 672 were randomized in a 1:1 ratio; 335 patients to the ribociclib arm and 337 patients to the placebo arm.

First patient enrolled: 20-Nov-2014.

Last patient randomized: 01-Aug-2016.

A total of 188 sites, across 30 countries enrolled patients. The countries (and respective number of sites) were as follows: Argentina (3), Australia (5), Belgium (4), Brazil (7), Bulgaria (3), Canada (6), Colombia (2), France (8), Germany (12), Greece (2), Hong Kong (3), Hungary (6),India (4), Italy (21), Republic of Korea (6), Lebanon (6), Malaysia (2), Mexico (3),Poland (2), Portugal (5), Russian Federation (2), Saudi Arabia (1), Singapore (2), Spain (17), Switzerland (1), Taiwan province of China (8), Thailand (2), Turkey (6), United Arab Emirates (1) and United States (38).

Conduct of the study

Protocol amendments

Amendment (Date)	Patients enrolled	Selected changes
1 (28-Apr-2015)	24	PFS assessment as per BIRC was changed from supportive analysis of the primary endpoint to a secondary endpoint.
2 (17-Feb-2016)	372	Central radiology assessment by medical oncologist review was replaced by a standard BIRC assessment.
3 (24-Jun-2016)	611	Eliminate the planned futility analysis since additional clinical data had been generated with ribociclib and other CDK 4/6 inhibitors compared to the start of the study providing additional assurance of the activity in patients with breast cancer. Include the change of approach for BIRC assessment of PFS from a full read to an audit (sample) based approach. Add an exploratory endpoint (PFS2) defined as the time from randomization to progression on next-line therapy or death, whichever occurred first, in order to make an exploratory assessment of longer-term benefit intermediate to PFS and OS.
4 (24-Feb-2017)	672	To remove the planned efficacy interim analysis: Interim analysis that allowed the study to stop for superior efficacy was planned after all patients had been randomized and approximately 80% PFS events (263 events) had been documented, as per local assessments.

Protocol deviations

Overall, 43.2% of patients reported at least one protocol deviation. The numbers of protocol deviations leading to exclusion from the per-protocol set (PPS) were low, with no imbalance between the two treatment arms. Overall, nine patients (1.3%) had protocol deviations which led to exclusion from the PPS; all deviations were due to the selection criteria not being met.

Table 27: Protocol deviations leading to exclusion from the Per-protocol set (FAS), Study E2301

Protocol deviation	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Any protocol deviation	**5 (1.5)**	**4 (1.2)**	**9 (1.3)**
Selection criteria not met	**5 (1.5)**	**4 (1.2)**	**9 (1.3)**
Criteria for measureable disease not met	3 (0.9)	1 (0.3)	4 (0.6)
Menopausal status not met (patient is neither pre- nor perimenopausal)	2 (0.6)	2 (0.6)	4 (0.6)
Criteria for prior therapy for advanced breast cancer not met	0	1 (0.3)	1 (0.1)

A patient with multiple protocol deviations within a category is counted only once in the category. Patients may have protocol deviations in more than one protocol deviation category

Baseline data

Table 28: Demographic characteristics (FAS) - Study E2301

Demographic variable	Ribociclib 600 mg N = 335	Placebo N = 337	All patients N = 672
Age (years)			
Mean (standard deviation)	42.6 (6.6)	43.7 (6.17)	43.1 (6.4)
Median (min-max)	43 (25 - 58)	45 (29 -58)	44 (25 -58)
Age category (years) - n (%)			
<40	98 (29.3)	88 (26.1)	186 (27.7)
≥ 40	237 (70.7)	249 (73.9)	486 (72.3)
Race - n (%)			
Caucasian	187 (55.8)	201 (59.6)	388 (57.7)
Asian	99 (29.6)	99 (29.4)	198 (29.5)
Black	10 (3.0)	9 (2.7)	19 (2.8)
Native American	3 (0.9)	3 (0.9)	6 (0.9)
Other	16 (4.8)	7 (2.1)	23 (3.4)
Unknown	20 (6.0)	18 (5.3)	38 (5.7)
Ethnicity - n (%)			
East Asian	62 (18.5)	69 (20.5)	131 (19.5)
Hispanic or Latino	49 (14.6)	43 (12.8)	92 (13.7)
West Asian	26 (7.8)	27 (8.0)	53 (7.9)
Southeast Asian	19 (5.7)	16 (4.7)	35 (5.2)
South Asian	9 (2.7)	8 (2.4)	17 (2.5)
Russian	5 (1.5)	3 (0.9)	8 (1.2)
Mixed ethnicity	1 (0.3)	2 (0.6)	3 (0.4)
Other	99 (29.6)	103 (30.6)	202 (30.1)
Not Reported	42 (12.5)	36 (10.7)	78 (11.6)
Unknown	23 (6.9)	30 (8.9)	53 (7.9)
Region - n (%)			
Europe and Australia	136 (40.6)	139 (41.2)	275 (40.9)
Asia	92 (27.5)	88 (26.1)	180 (26.8)
North America	47 (14.0)	50 (14.8)	97 (14.4)
Latin America	31 (9.3)	25 (7.4)	56 (8.3)
Other	29 (8.7)	35 (10.4)	64 (9.5)
ECOG performance status – n (%) at baseline			
0	245 (73.1)	255 (75.7)	500 (74.4)
1	87 (26.0)	78 (23.1)	165 (24.6)
2	0	1 (0.3)	1 (0.1)
Missing	3 (0.9)	3 (0.9)	6 (0.9)

Table 29: Disease characteristics (FAS) - Study E2301

Disease characteristics	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Primary site of cancer – n (%)			
Breast	335 (100.0)	337 (100.0)	672 (100.0)
Histological grade – n (%)			
Well differentiated	28 (8.4)	26 (7.7)	54 (8.0)
Moderately differentiated	146 (43.6)	145 (43.0)	291 (43.3)
Poorly differentiated	91 (27.2)	92 (27.3)	183 (27.2)
Undifferentiated	1 (0.3)	4 (1.2)	5 (0.7)
Unknown	68 (20.3)	70 (20.8)	138 (20.5)
Missing	1 (0.3)	0	1 (0.1)
Stage at initial diagnosis – n (%)			
0	4 (1.2)	3 (0.9)	7 (1.0)
I	24 (7.2)	30 (8.9)	54 (8.0)
II	91 (27.2)	89 (26.4)	180 (26.8)
III	69 (20.6)	66 (19.6)	135 (20.1)
IV	140 (41.8)	135 (40.1)	275 (40.9)
Unknown	7 (2.1)	14 (4.2)	21 (3.1)
Disease status at study entry– n (%)			
Locally advanced	1 (0.3)	1 (0.3)	2 (0.3)
Distant metastatic	334 (99.7)	336 (99.7)	670 (99.7)
Disease free interval - n (%) [1]			
De novo	136 (40.6)	134 (39.8)	270 (40.2)
Non de novo	199 (59.4)	203 (60.2)	402 (59.8)
≤ 12 months	23 (6.9)	13 (3.9)	36 (5.4)
>12 months	176 (52.5)	190 (56.4)	366 (54.5)
Types of lesions at baseline-n (%)			
Both target and non-target	244 (72.8)	247 (73.3)	491 (73.1)
Non-target only	66 (19.7)	62 (18.4)	128 (19.0)
Target only	25 (7.5)	28 (8.3)	53 (7.9)
Current extent of disease (metastatic sites) – n (%)			
Bone	251 (74.9)	247 (73.3)	498 (74.1)
Bone only metastasis	81 (24.2)	78 (23.1)	159 (23.7)
Visceral	193 (57.6)	188 (55.8)	381 (56.7)
Lung or Liver	173 (51.6)	170 (50.4)	343 (51.0)
Liver	105 (31.3)	115 (34.1)	220 (32.7)
Lung	106 (31.6)	88 (26.1)	194 (28.9)
Other [2]	53 (15.8)	42 (12.5)	95 (14.1)
Lymph nodes	142 (42.4)	158 (46.9)	300 (44.6)
Soft Tissue	25 (7.5)	21 (6.2)	46 (6.8)
Skin	8 (2.4)	8 (2.4)	16 (2.4)
None	1 (0.3)	0	1 (0.1)
Number of metastatic sites - n (%)			
0	1 (0.3)	0	1 (0.1)
1	112 (33.4)	117 (34.7)	229 (34.1)
2	106 (31.6)	99 (29.4)	205 (30.5)
3	61 (18.2)	75 (22.3)	136 (20.2)
4	41 (12.2)	32 (9.5)	73 (10.9)
≥ 5	14 (4.2)	14 (4.2)	28 (4.2)

[1] De novo includes patients with no first recurrence/progression or first recurrence/progression within 90 days of diagnosis with no prior antineoplastic medication. For non-de novo patients, DFI is the time from initial diagnosis to first recurrence/progression.
[2] Other visceral includes any metastatic site other than soft tissue, bone, lung, liver, skin, and lymph nodes

Table 30: Endocrine therapy and receptor status - Study E2301

Disease history	Ribociclib 600 mg	Placebo	All patients
	N = 335	N = 337	N = 672
(Neo-) adjuvant endocrine therapy – (n%)			
No prior (neo-) adjuvant endocrine therapy	208 (62.1)	196 (58.2)	404 (60.1)
Progression on or within 12 months of end of endocrine therapy	100 (29.9)	105 (31.2)	205 (30.5)
Progression >12 months after end of endocrine therapy	25 (7.5)	35 (10.4)	60 (8.9)
Missing[1]	2 (0.6)	1 (0.3)	3 (0.4)
(Neo-) adjuvant endocrine therapy – (n%)			
HER2 receptor status – n (%)			
Negative	335 (100.0)	337 (100.0)	672 (100.0)
Estrogen receptor status – n (%)			
Positive	331 (98.8)	335 (99.4)	666 (99.1)
Negative	4 (1.2)	2 (0.6)	6 (0.9)
Progesterone receptor status – n (%)			
Positive	290 (86.6)	288 (85.5)	578 (86.0)
Negative	45 (13.4)	49 (14.5)	94 (14.0)
Estrogen and/or progesterone receptor status – n (%)			
At least one positive	335 (100.0)	337 (100.0)	672 (100.0)

[1]Missing includes patients with prior (neo-) adjuvant endocrine therapy without a corresponding end date.

Table 31: Prior antineoplastic therapy (Abbreviated) - Study E2301

Characteristics	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Medication: chemotherapy setting[1]			
Adjuvant	109 (32.5)	110 (32.6)	219 (32.6)
Neoadjuvant	60 (17.9)	61 (18.1)	121 (18.0)
Therapeutic	47 (14.0)	47 (13.9)	94 (14.0)
Medication: hormonal therapy setting[1]			
Adjuvant	126 (37.6)	140 (41.5)	266 (39.6)
Neoadjuvant	2 (0.6)	3 (0.9)	5 (0.7)
Therapeutic	1 (0.3)	3 (0.9)	4 (0.6)

Table 32: Randomization by stratification factor (FAS) - Study E2301

Stratification factor at randomization	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Lung and/or liver metastases			
Yes	171 (51.0)	173 (51.3)	344 (51.2)
No	164 (49.0)	164 (48.7)	328 (48.8)
Prior chemotherapy for advanced disease			
Yes	60 (17.9)	60 (17.8)	120 (17.9)
No	275 (82.1)	277 (82.2)	552 (82.1)
Endocrine combination partner			
NSAI and goserelin	245 (73.1)	248 (73.6)	493 (73.4)
Tamoxifen and goserelin	90 (26.9)	89 (26.4)	179 (26.6)

Strata as entered in the IRT during randomization

Numbers analysed

Table 33: Analysis sets (All randomized patients) - Study E2301

Analysis population	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Full Analysis Set	335 (100)	337 (100)	672 (100)
Safety Set	335 (100)	337 (100)	672 (100)
Per-Protocol Set	330 (98.5)	333 (98.8)	663 (98.7)
Pharmacokinetic analysis set	260 (77.6)	238 (70.6)	498 (74.1)

Outcomes and estimation

Data cut-off date for primary analysis: 20-Aug-2017.

As of the data cut-off date, the median time from randomization to the data cut-off date was 19.2 months.

Primary endpoint: PFS per investigator

Table 34: PFS per investigator assessment (FAS) - Study E2301

Category	Ribociclib 600 mg N = 335	Placebo N = 337
Number of events - n (%)	**131 (39.1)**	**187 (55.5)**
Progression	128 (38.2)	183 (54.3)
Death[1]	3 (0.9)	4 (1.2)
Number censored - n (%)	204 (60.9)	150 (44.5)
p-value ribociclib vs. placebo[2]	9.83×10^{-8}	
Hazard ratio (95% CI) ribociclib vs. placebo[3]	**0.553 (0.441, 0.694)**	
Percentiles (95% CI)		
25th	10.6 (7.4, 12.8)	5.6 (3.6, 7.2)
Median	23.8 (19.2, NE)	13.0 (11.0, 16.4)
75th	NE (27.5, NE)	NE (24.2, NE)
Kaplan-Meier estimate (95% CI)		
Month 6	82.8 (78.2, 86.5)	72.8 (67.7, 77.4)
Month 12	71.5 (66.2, 76.2)	54.5 (48.8, 59.8)
Month 18	58.2 (51.9, 64.0)	40.5 (34.5, 46.4)
Month 24	49.1 (40.1, 57.4)	32.6 (25.4, 39.9)

NE=not estimable

[1] Death before progression

[2] One-sided p-value obtained from log-rank test stratified by liver and/or lung metastases prior chemotherapy for advanced disease, and endocrine combination partner per IRT

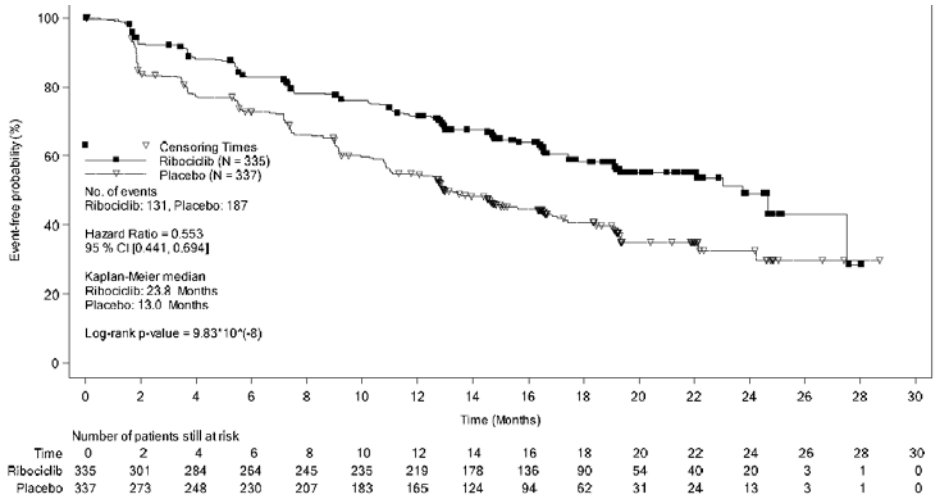


Figure 14: Kaplan-Meier plot of PFS per investigator (FAS) - Study E2301

Key secondary endpoint: OS

The pre-specified efficacy stopping boundary was not crossed at the first interim OS analysis. Fewer (89) than expected (123) deaths had occurred.

Table 35: Analysis of OS using log-rank test, Cox model and Kaplan-Meier method (FAS) - Study E2301

Category	Ribociclib 600 mg N=335	Placebo N=337
Number of events - n (%)	43 (12.8)	46 (13.6)
Number censored - n (%)	292 (87.2)	291 (86.4)
p-value ribociclib vs. placebo[1]	0.341	
Hazard ratio (95% CI) ribociclib vs. placebo[2]	0.916 (0.601, 1.396)	

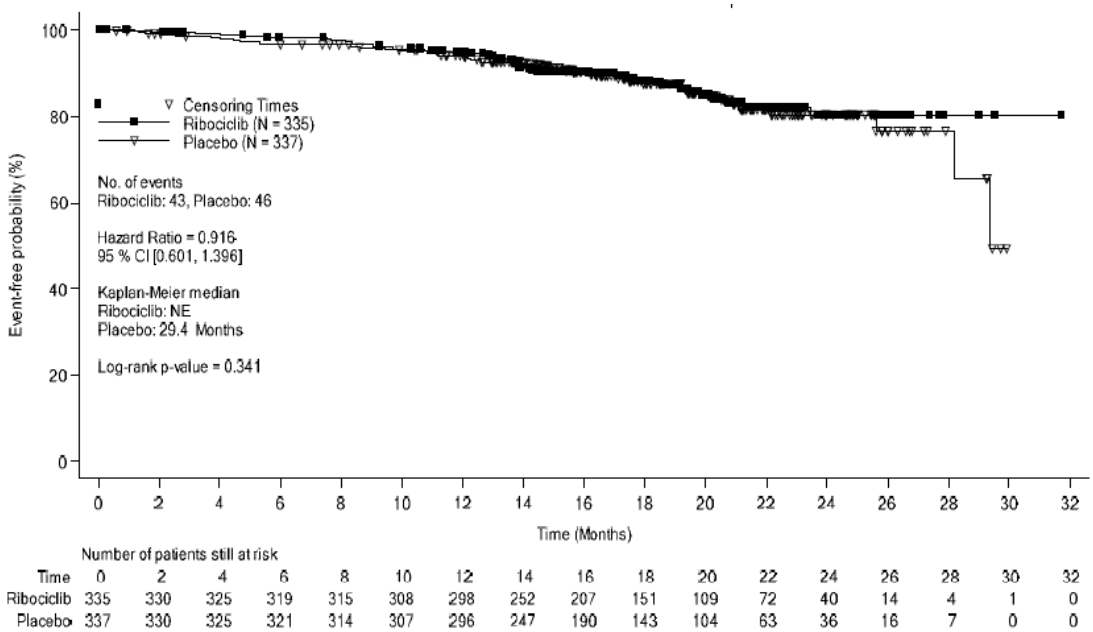


Figure 15: Kaplan-Meier plot of overall survival (FAS) - Study E2301

Other secondary efficacy results

- Best overall response per Investigator assessment

Table 36: Best overall response per Investigator assessment (FAS) - Study E2301

	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	P-value
Patients with measurable disease at baseline	269 (80.3)	275 (81.6)	
Patients with non-measurable disease at baseline	66 (19.7)	62 (18.4)	
Best Overall Response			
Complete response (CR)	8 (2.4)	7 (2.1)	
Partial response (PR)	129 (38.5)	93 (27.6)	
Stable disease	106 (31.6)	120 (35.6)	
Non-CR/Non-PD	60 (17.9)	53 (15.7)	
Progressive disease (PD)	24 (7.2)	52 (15.4)	
Unknown (UNK)	8 (2.4)	12 (3.6)	
Overall Response Rate (ORR) – n (%)	137 (40.9)	100 (29.7)	9.80×10^{-4}
95% CI	(35.6, 46.2)	(24.8, 34.6)	
Clinical Benefit Rate (CBR) – n (%)	265 (79.1)	235 (69.7)	0.002
95% CI	(74.8, 83.5)	(64.8, 74.6)	

N is the denominator for percentage calculation.
The 95% CI for the frequency distribution of each variable was computed using normal approximation
ORR = proportion of patients with confirmed CR or PR
CBR = proportion of patients with confirmed CR or PR, or (SD or Non-CR/Non-PD≥ 24 weeks)
P-values are based on the Cochran-Mantel Haenszel chi-square test (strata based on IRT data)

- Duration of response

Among patients with confirmed CR or PR the median duration of response was longer for patients in the ribociclib arm (21.3 months; 95% CI: 18.3, NE) compared to the placebo arm (17.5 months; 95% CI: 12.0, NE). The estimated probability of maintaining response for at least 12 months was 79.2% (95% CI: 70.5, 85.6) in the ribociclib arm and 58.7% (95% CI: 47.4, 68.3) in the placebo arm.

- Patient reported outcomes

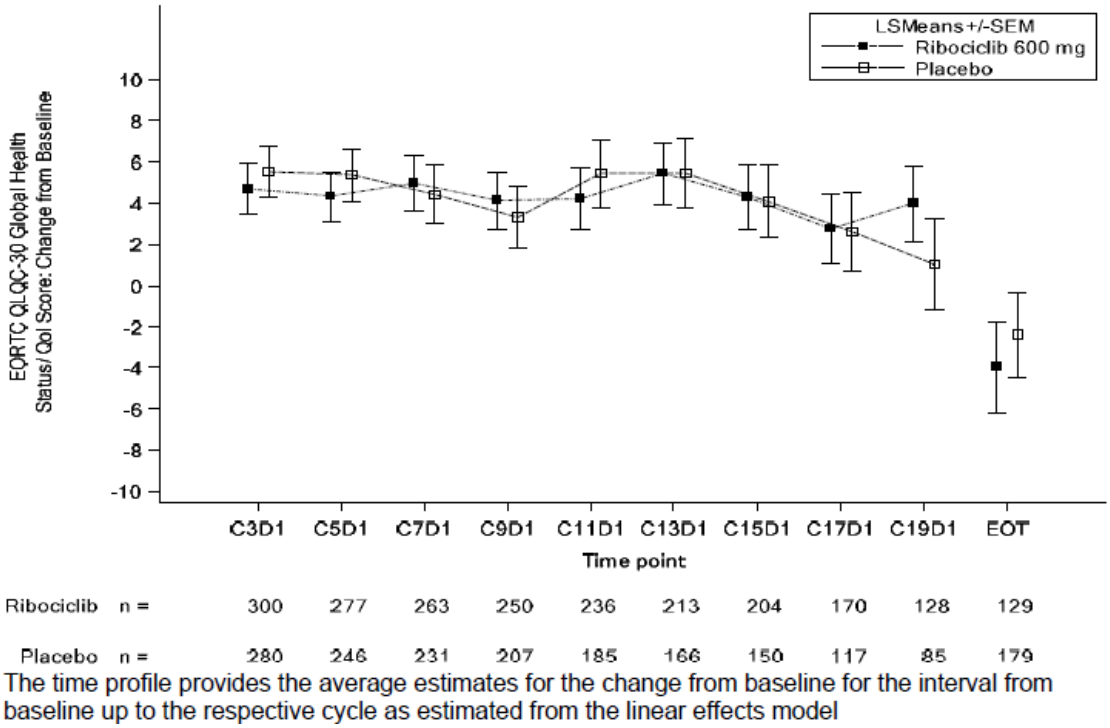


Figure 16: Summary of change from Baseline in global health patient reported outcomes by treatment- Global health status/QoL scale score of EORTC QLQ-C30 questionnaire (FAS) - Study E2301

Time to definitive deterioration in ECOG PS showed no differences between the two treatment arms with an HR of 0.781 (95% CI: 0.524, 1.166; one sided p = 0.113), with only 47 and 51 events in the respective arms.

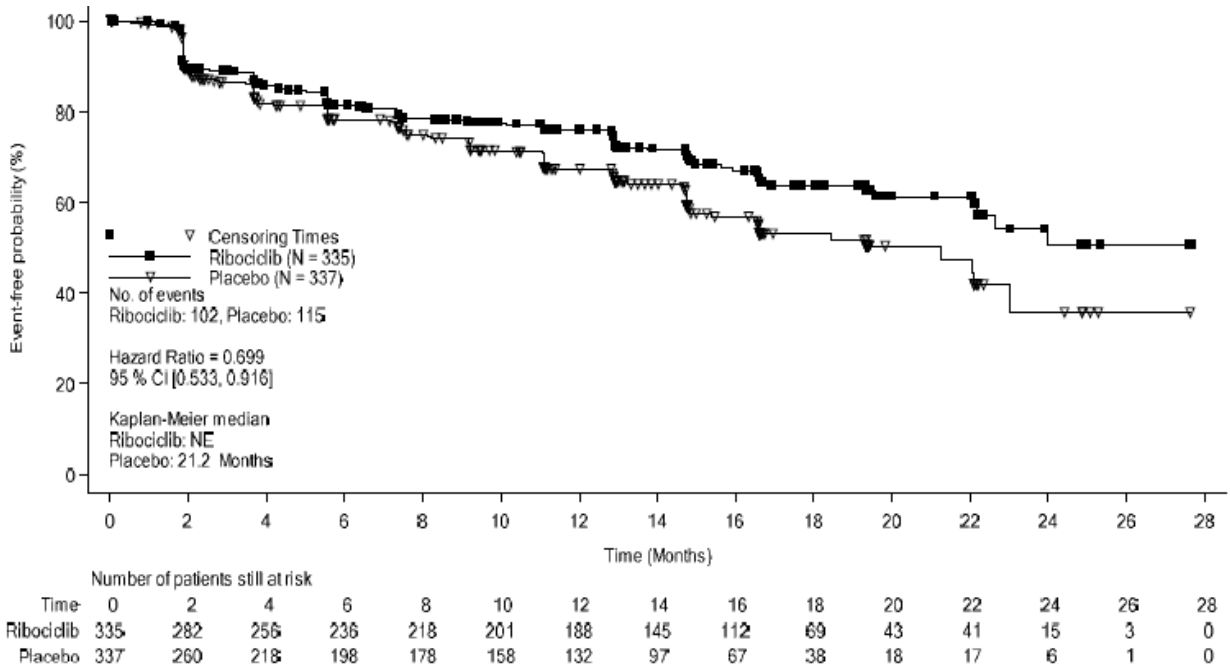


Figure 17: Kaplan-Meier plot of time to definitive 10 percent deterioration in EORTC QLQ-C30 global health status scale score (FAS) - Study E2301

Exploratory endpoints:

- PFS2

Table 37: Stratified Cox regression model for PFS2 (months) Full Analysis Set - Study E2301

	Events/N (%)	Median Time (95% CI) (months) [1]	Cox model [2] Hazard ratio [3]	95% CI
All patients				
Placebo	72/337 (21.4)	NE (28.2, NE)		
Ribociclib 600 mg	63/335 (18.8)	NE (27.9, NE)	0.841	(0.598, 1.183)

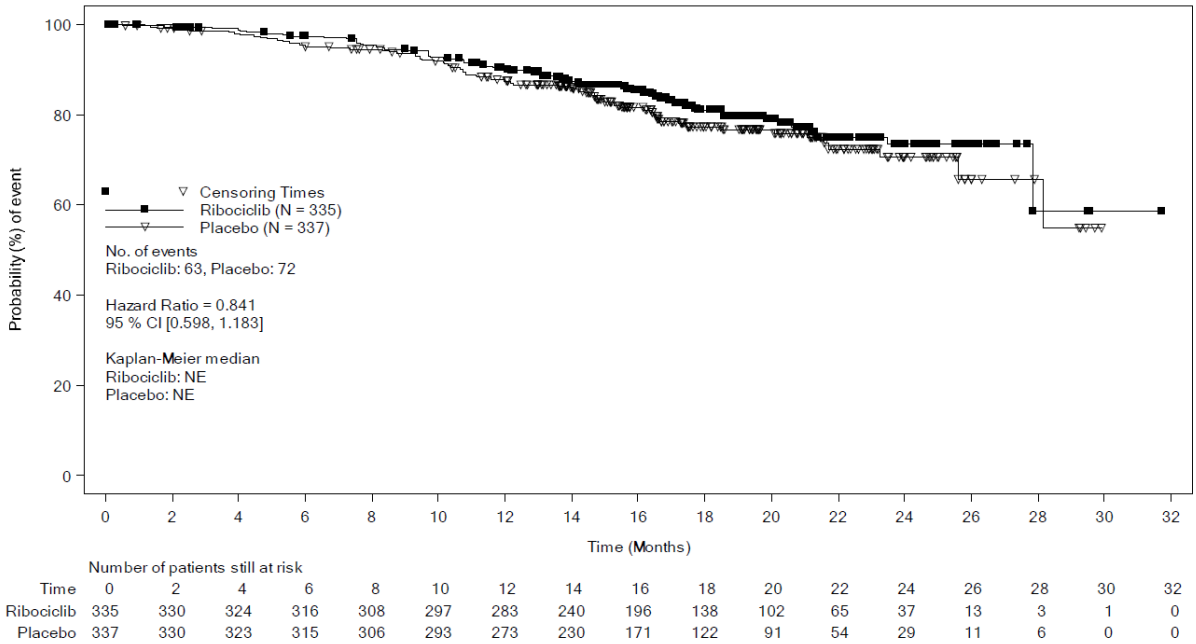


Figure 18: Kaplan-Meier plot of PFS2 by treatment Full Analysis Set - Study E2301

Table 38: Type of events for PFS2 Full Analysis Set- Study E2301

	Ribociclib 600 mg N=335 n (%)	Placebo N=337 n (%)
Number of PFS2 events	63 (18.8)	72 (21.4)
Progression	31 (9.3)	43 (12.8)
Clinical	3 (0.9)	6 (1.8)
Radiological	28 (8.4)	37 (11.0)
Death	32 (9.6)	29 (8.6)
Death prior to next line therapy	14 (4.2)	18 (5.3)
Death on next line therapy	18 (5.4)	11 (3.3)
Number censored	272 (81.2)	265 (78.6)

Table 39: Reasons for censoring in PFS2 Full Analysis Set- Study E2301

Reason of censoring	Ribociclib 600 mg N=335 n(%)	Placebo N=337 n(%)
Number of patients censored	272 (81.2)	265 (78.6)
Reason of censoring		
Lost to follow-up (1)	20 (6.0)	21 (6.2)
No next-line therapy initiated	203 (60.6)	158 (46.9)
Next-line therapy initiated with no second next-line therapy	45 (13.4)	83 (24.6)
Second next-line therapy initiated	4 (1.2)	3 (0.9)

Ancillary analyses

- Sensitivity analyses of PFS per investigator assessment

Table 40: Sensitivity analysis of PFS per local Investigator assessment (FAS) - Study E2301

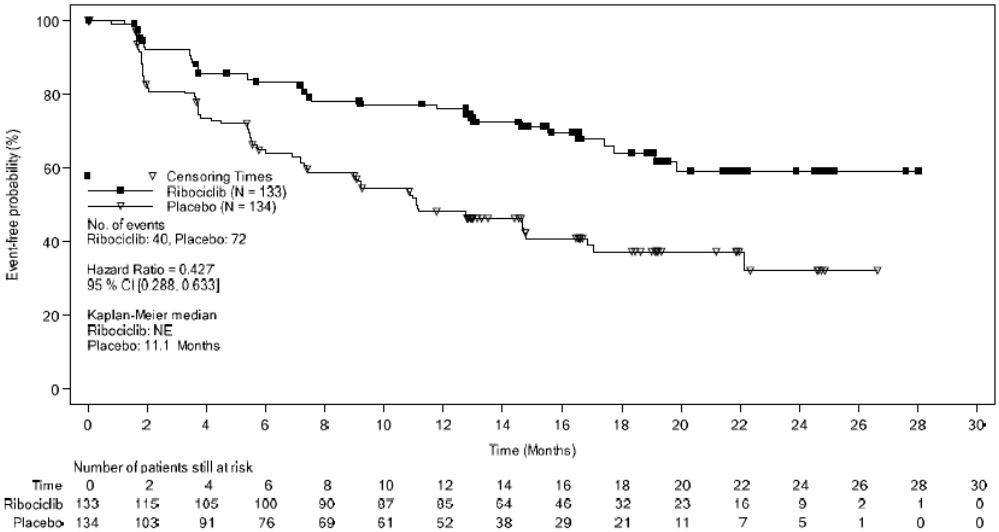
Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)
Primary analysis			
Ribociclib 600 mg	23.8 (19.2, NE)	9.83×10^{-8}	0.553 (0.441, 0.694)
Placebo	13.0 (11.0, 16.4)		
Unstratified log-rank test and Cox model			
Ribociclib 600 mg	23.8 (19.2, NE)	3.85×10^{-7}	0.573 (0.458, 0.716)
Placebo	13.0 (11.0, 16.4)		
Stratified Cox model, adjusting for baseline covariates [1]			
Ribociclib 600 mg	23.8 (19.2, NE)	9.83×10^{-8}	0.516 (0.410, 0.651)
Placebo	13.0 (11.0, 16.4)		
'Actual event' [2]			
Ribociclib 600 mg	23.8 (19.2, NE)	1.62×10^{-7}	0.562 (0.449, 0.703)
Placebo	12.9 (11.0, 16.4)		
'Backdating' [3]			
Ribociclib 600 mg	23.8 (19.2, NE)	7.36×10^{-8}	0.553 (0.442, 0.692)
Placebo	12.9 (10.9, 15.6)		
'Censoring for antineoplastic therapy' [4]			
Ribociclib 600 mg	23.8 (19.4, NE)	1.21×10^{-7}	0.551 (0.438, 0.693)
Placebo	13.3 (11.1, 16.5)		

CI Confidence interval; PFS Progression-free survival
[1] Baseline covariates included in the Cox proportional hazard model are ECOG performance status (0 vs. ≥ 1), bone only lesion at baseline (yes vs. no), age (< 40 vs. ≥ 40 years), and prior (neo-)adjuvant endocrine therapy (ET) (none; yes – progression while on or within 12 months of end of (neo-)adjuvant ET; yes –progression > 12 months after end of (neo-)adjuvant ET)
[2] Analysis includes the event whenever it occurred even after ≥ 2 missing tumor assessments
[3] Analysis uses the date of the next scheduled assessment for events occurring after ≥ 1 missing assessment
[4] Analysis performed by censoring patients at start of new antineoplastic therapy
p-values make no adjustment for multiple testing

- PFS per BIRC review in audit sample

Table 41: Progression-free survival per BIRC review for audited patients using Cox model and Kaplan-Meier methodology (FAS) - Study E2301

Category	Ribociclib 600 mg N = 133	Placebo N = 134
Number of events - n (%)	40 (30.1)	72 (53.7)
Progression	39 (29.3)	71 (53.0)
Death[1]	1 (0.8)	1 (0.7)
Number censored - n (%)	93 (69.9)	62 (46.3)
Hazard ratio (95% CI) ribociclib vs. placebo[2]	0.427 (0.288, 0.633)	



Cox model is stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

Figure 19: Kaplan-Meier plot of progression-free survival based on central BIRC review for audited patients (FAS) - Study E2301

- Concordance in PFS by investigator and BIRC

Table 42: Early and late discrepancy rates and differential discordance of progression status per investigator and BIRC Full Analysis Set - Study E2301

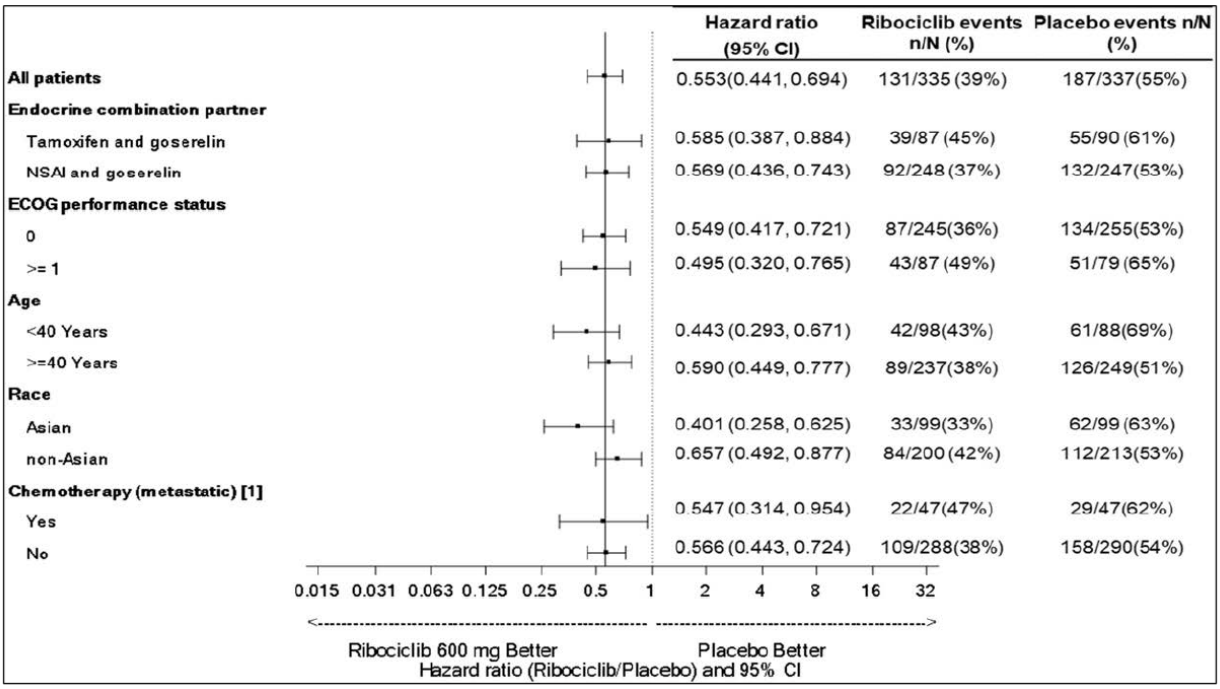
Progression per investigator (INV)	Progression per BIRC	Timing	Ribociclib 600 mg N=133	Placebo N=134
PD	PD	Same time (a1)	20	34
PD	PD	INV after BIRC (a2)	13	27
PD	PD	INV before BIRC (a3)	1	1
PD	PD	Total (a)	34	62
PD	No PD	Total (b)	14	15
No PD	PD	Total (c)	5	9
No PD	No PD	Total (d)	80	48
Early discrepancy rate (EDR): (b+a3)/(a+b)			0.313	0.208
Differential discordance of EDR			0.105	
Late discrepancy rate (LDR): (c+a2)/(b+c+a2+a3)			0.545	0.692
Differential discordance of LDR			-0.147	

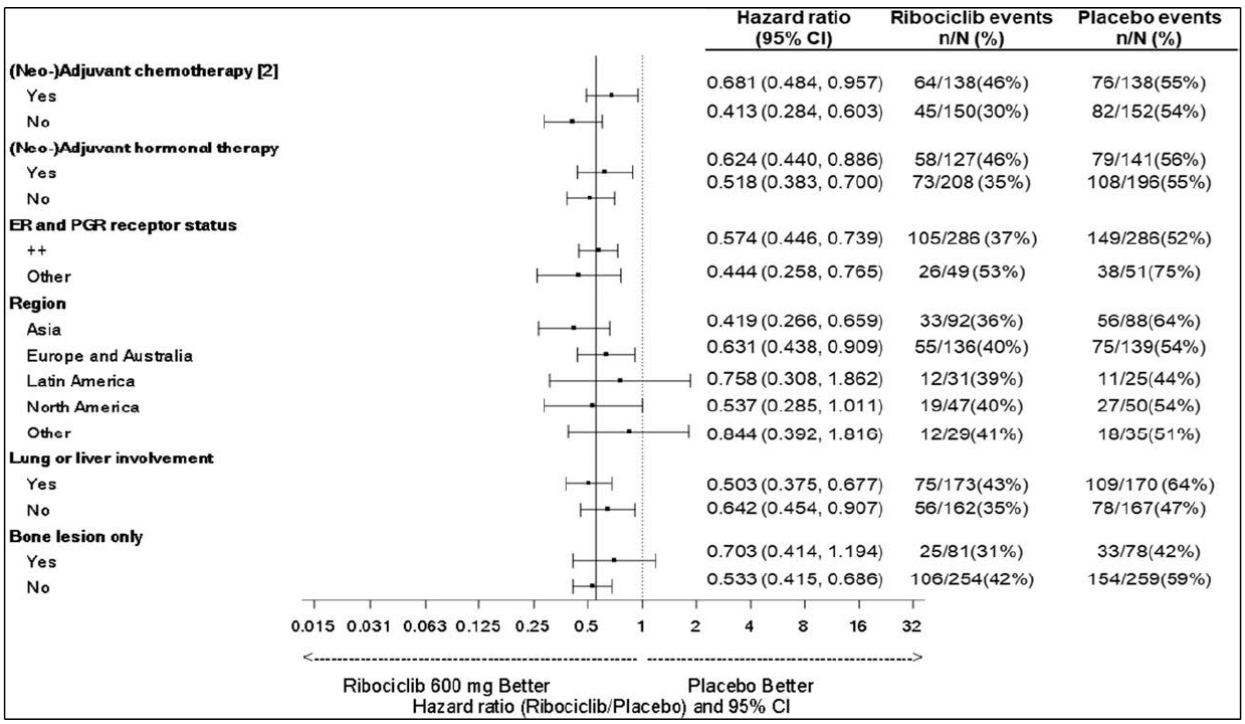
- Progression-free survival censoring reasons

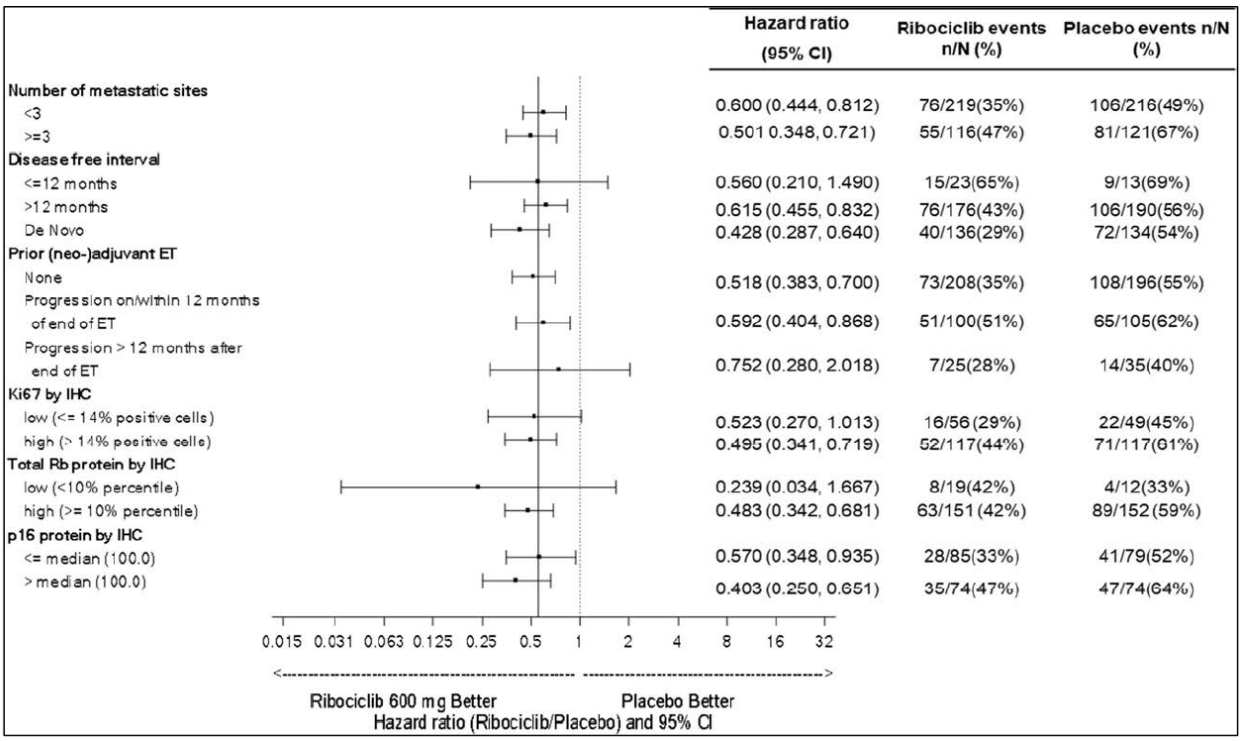
Table 43: Progression-free survival censoring reasons per Investigator assessment and BIRC review (FAS) - Study E2301

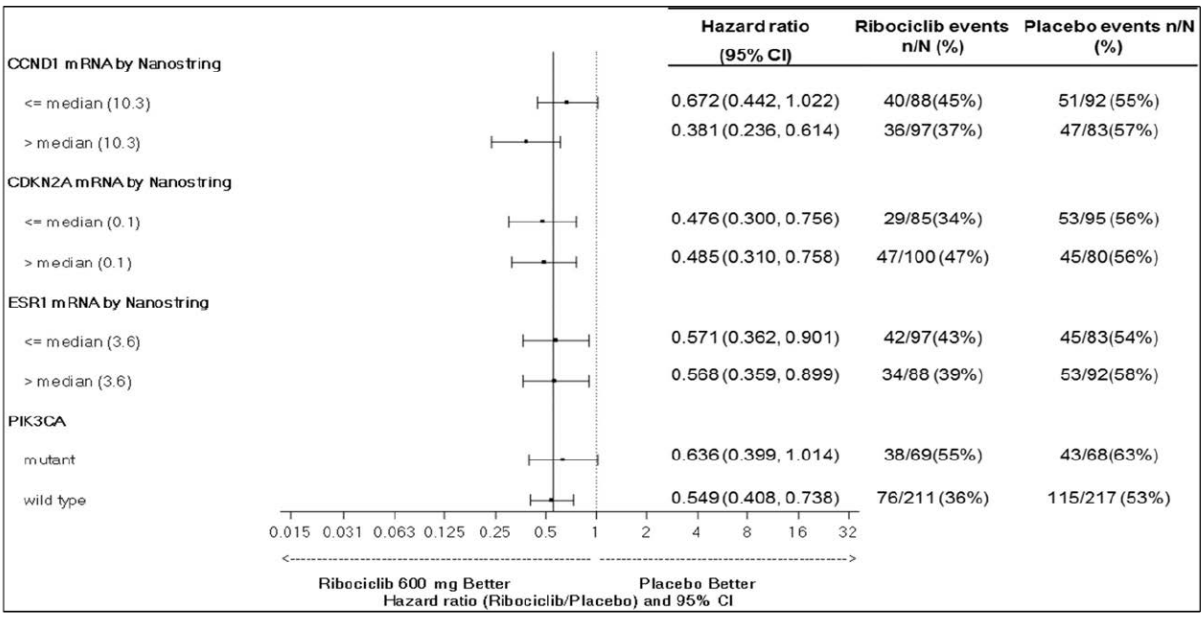
	Investigator assessment		BIRC review#	
	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	Ribociclib 600 mg N = 133 n (%)	Placebo N = 134 n (%)
Number of patients censored	**204 (60.9)**	**150 (44.5)**	**93 (69.9)**	**62 (46.3)**
Reason of censoring				
Ongoing without event[1]	176 (52.5)	120 (35.6)	72 (54.1)	42 (31.3)
Adequate assessment no longer available[2]	15 (4.5)	17 (5.0)	17 (12.8)	14 (10.4)
Withdrew consent	9 (2.7)	9 (2.7)	2 (1.5)	3 (2.2)
Event documented after two or more missing tumor assessments	2 (0.6)	4 (1.2)	2 (1.5)	3 (2.2)
Lost to follow-up[3]	2 (0.6)	0	0	0

- PFS in subgroups









[1] Prior chemotherapy in metastatic setting
[2] Adjuvant or neo-adjuvant chemotherapy in patients with no prior chemotherapy in metastatic setting
Dotted line shows no effect point, solid line shows overall treatment effect point.
Hazard ratio (95% CI) is based on stratified Cox PH model. Exception: for subgroups based on lung/liver involvement, endocrine combination partner, and prior chemotherapy in metastatic setting unstratified Cox PH model is used.

Figure 20: Forest plot of hazard ratio with 95% confidence interval for PFS based on local Investigator's assessment from subgroup analysis (FAS) - Study E2301

- PFS by endocrine combination partner

The efficacy results in patients that received NSAI and goserelin as endocrine backbone are presented below.

Table 44: Progression-free survival per Investigator assessment by endocrine combination partner (FAS) - Study E2301

Category	Combination partner: NSAI and goserelin		Combination partner: Tamoxifen and goserelin	
	Ribociclib 600 mg	Placebo	Ribociclib 600 mg	Placebo
	N=248	N=247	N=87	N=90
Number of events – n (%)	92 (37.1)	132 (53.4)	**39 (44.8)**	**55 (61.1)**
Progression	92 (37.1)	129 (52.2)	36 (41.4)	54 (60.0)
Death [1]	0	3 (1.2)	3 (3.4)	1 (1.1)
Number censored – n (%)	156 (62.9)	115 (46.6)	48 (55.2)	35 (38.9)
Hazard ratio (95% CI) ribociclib vs. Placebo [2]	**0.569 (0.436, 0.743)**		**0.585 (0.387, 0.884)**	

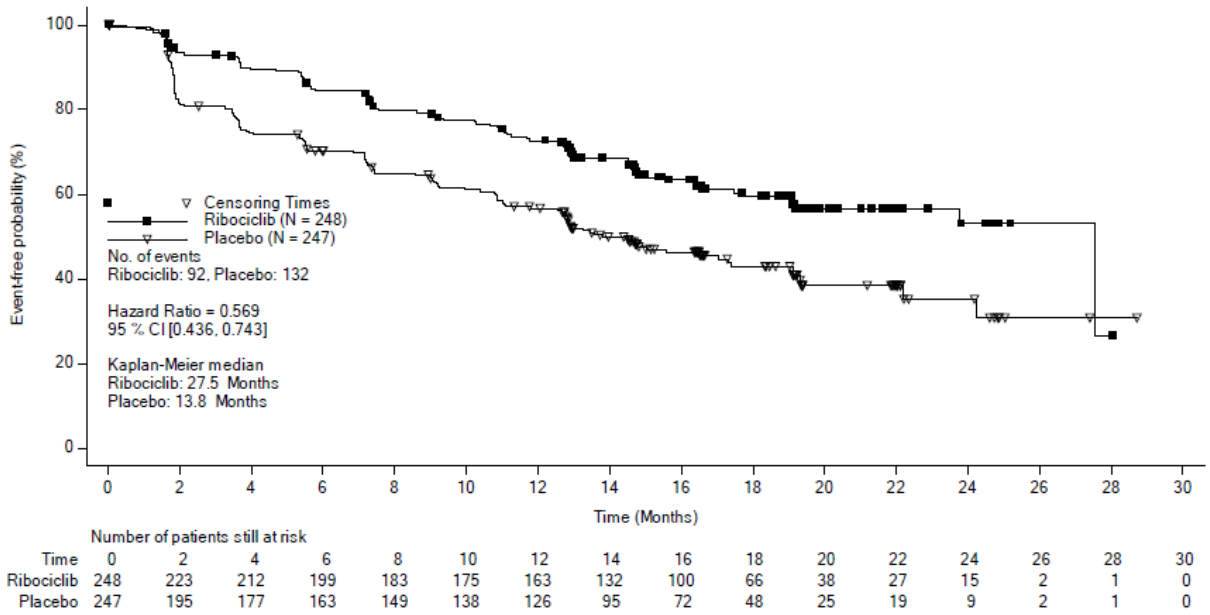


Figure 21: Kaplan-Meier plot of progression-free survival per Investigator assessment by endocrine combination partner-NSAI (FAS) - Study E2301

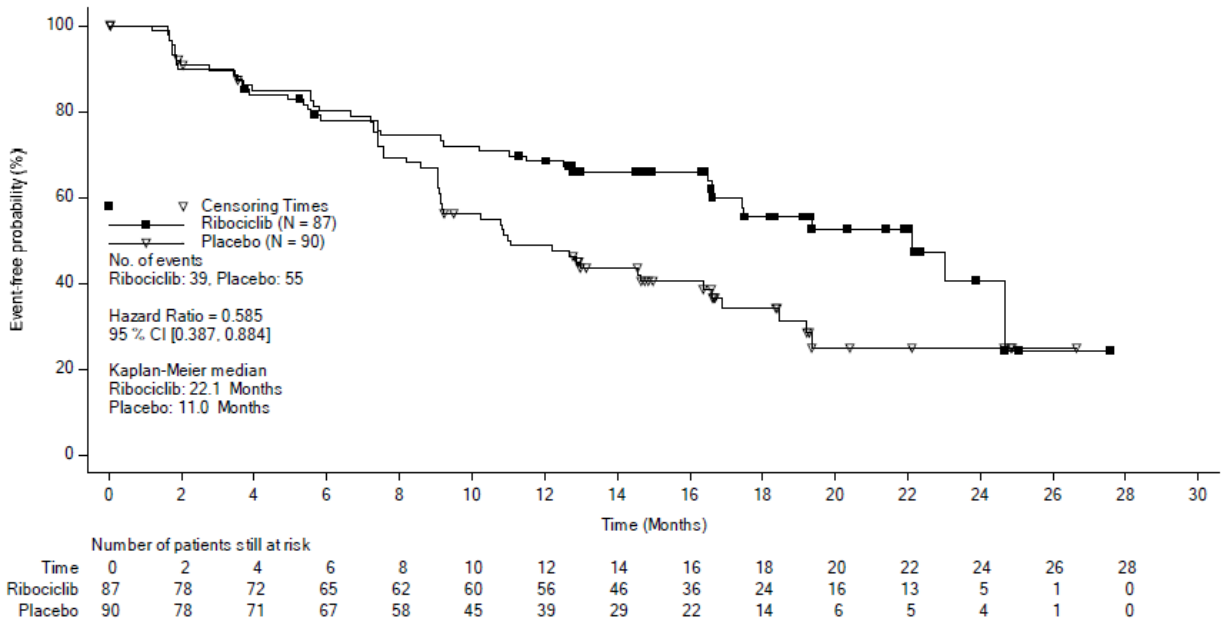
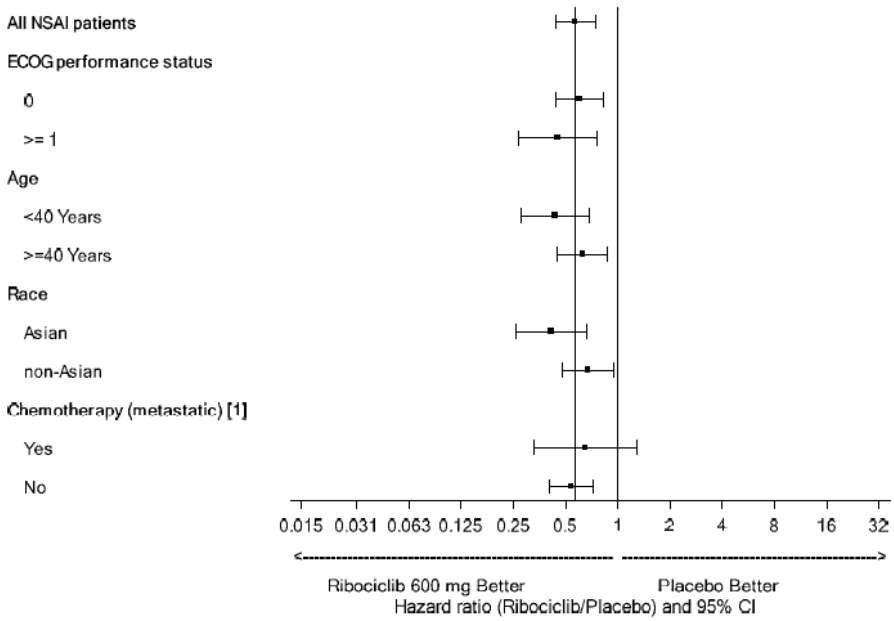


Figure 22: Kaplan-Meier plot of progression-free survival per Investigator assessment by endocrine combination partner-Tamoxifen (FAS) - Study E2301

- PFS: subgroups analysis within combination partner NSAI



[1] Prior chemotherapy in metastatic setting; [2] Adjuvant or neo-adjuvant chemotherapy in patients with no prior chemotherapy in metastatic setting
Dotted line shows no effect point, solid line shows overall treatment effect point within the NSAI subgroup.
Hazard ratio (95% CI) is based on unstratified Cox PH model.

Figure 23: Forest plot of hazard ratio with 95% confidence interval for PFS based on local investigator assessment from subgroup analyses within combination partner NSAI Full Analysis Set - Study E2301

- OS analysis by endocrine partner

Overall survival data were not mature at the time of the data cutoff date in the full population or in either of endocrine combination subgroups. Collection of survival data is continuing. In patients with NSAI as the endocrine combination partner, 30/248 (12.1) patients and 36/247 (14.6) patients in the ribociclib arm and placebo arm died, respectively, with an HR of 0.798 (95% CI: 0.491, 1.295). In patients with tamoxifen as combination partner, there were 13/87 (14.9%) and 10/90 (11.1%) deaths in the ribociclib and placebo arms, respectively, with an HR of 1.384 (95% CI: 0.607, 3.158).

- Best overall response per local investigator's assessment - subgroup

Table 45: Best overall response per local investigator's assessment - subgroup: patients with NSAI as combination partner Full Analysis Set - Study E2301

	Ribociclib 600 mg N=248		Placebo N=247		Difference between treatment groups	
	n (%)	95% CI	n (%)	95% CI	Difference	95% CI
Patients with measurable disease at baseline	192 (77.4)		199 (80.6)			
Patients with non-measurable disease only at baseline	56 (22.6)		48 (19.4)			
Best Overall Response						
Complete Response (CR)	7 (2.8)		4 (1.6)			
Partial Response (PR)	90 (36.3)		68 (27.5)			
Stable Disease (SD)	77 (31.0)		82 (33.2)			
Non-CR/Non-PD	51 (20.6)		41 (16.6)			
Progressive Disease (PD)	17 (6.9)		43 (17.4)			
Unknown (UNK)	6 (2.4)		9 (3.6)			
Overall Response Rate (ORR: CR+PR)	97 (39.1)	(33.0, 45.2)	72 (29.1)	(23.5, 34.8)	9.96	(1.7, 18.3)
Clinical Benefit Rate (CBR: CR+PR+(SD+Non-CR / Non-PD>=24 weeks))	199 (80.2)	(75.3, 85.2)	166 (67.2)	(61.4, 73.1)	13.0	(5.4, 20.7)

Table 46: Best overall response per local investigator's assessment - subgroup: patients with tamoxifen as combination partner Full Analysis Set - Study E2301

	Ribociclib 600 mg N=87		Placebo N=90		Difference between treatment groups	
	n (%)	95% CI	n (%)	95% CI	Difference	95% CI
Patients with measurable disease at baseline	77 (88.5)		76 (84.4)			
Patients with non-measurable disease only at baseline	10 (11.5)		14 (15.6)			
Best Overall Response						
Complete Response (CR)	1 (1.1)		3 (3.3)			
Partial Response (PR)	39 (44.8)		25 (27.8)			
Stable Disease (SD)	29 (33.3)		38 (42.2)			
Non-CR/Non-PD	9 (10.3)		12 (13.3)			
Progressive Disease (PD)	7 (8.0)		9 (10.0)			
Unknown (UNK)	2 (2.3)		3 (3.3)			
Overall Response Rate (ORR: CR+PR)	40 (46.0)	(35.5, 56.4)	28 (31.1)	(21.5, 40.7)	14.9	(0.7, 29.0)

Clinical Benefit Rate (CBR: CR+PR+(SD+Non-CR / Non-PD>=24 weeks))	66	(75.9)	(66.9, 84.9)	69 (76.7)	(67.9, 85.4)	-.80 (-13.3, 11.7)

- Best overall response per BIRC review in audit sample

Table 47: Best overall response as per BIRC assessment for audit sample of patients (FAS) - Study E2301

	Ribociclib 600 mg	Placebo
	N = 133	N = 134
Best Overall Response -n (%)		
Complete Response (CR)	4 (3.0)	1 (0.7)
Partial Response (PR)	57 (42.9)	37 (27.6)
Stable Disease	28 (21.1)	30 (22.4)
Non-CR/Non-PD	30 (22.6)	37 (27.6)
Progressive Disease (PD)	9 (6.8)	24 (17.9)
Unknown (UNK)	5 (3.8)	5 (3.7)
Overall Response Rate (ORR) -n (%)	**61 (45.9)**	**38 (28.4)**
95% CI	(37.4, 54.3)	(20.7, 36.0)
Clinical Benefit Rate (CBR) -n (%)	**101 (75.9)**	**82 (61.2)**
95% CI	(68.7, 83.2)	(52.9, 69.4)

N is the denominator for percentage calculation.
The 95% CI for the frequency distribution of each variable was computed using normal approximation
ORR = proportion of patients with confirmed CR or PR
CBR = proportion of patients with confirmed CR or PR, or (SD or Non-CR/Non-PD≥ 24 weeks)
P-values are based on the Cochran-Mantel Haenszel chi-square test (strata based on IRT data)
Source: Table 14.2-1.26

Study F2301 – MONALEESA-3

A randomized double-blind, placebo controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.

Methods

Study participants

Key inclusion criteria
- Adult male/female ≥ 18 years old. - Female patients had to be post-menopausal (bilateral oophorectomy, ≥ 60, < 60 and amenorrheic ≥ 12 months). - Histologically or cytologically HR and/or PgR positive. - HER2 negative. - Patients with either Measurable disease i.e. at least one measurable lesion per Response Evaluation Criteria OR If no measurable disease was evident then at least one predominantly lytic bone lesion was to be present in solid tumors (RECIST 1.1) - Patients with advanced (loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or radiotherapy) or metastatic) breast cancer. Patients could be: a. Newly diagnosed advanced/metastatic breast cancer, treatment naïve.

b. Relapsed with documented evidence of relapse more than 12 months from completion of (neo) adjuvant endocrine therapy with no treatment for advanced/metastatic disease.

c. Relapsed with documented evidence of relapse on or within 12 months from completion of (neo) adjuvant endocrine therapy with no treatment for advanced/metastatic disease.

d. Relapsed with documented evidence of relapse more than 12 months from completion of (neo) adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-estrogen or an AI) for advanced/metastatic disease.

e. Advanced/metastatic breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-estrogen or an AI).

Note: Patients who relapsed with documented evidence of relapse on/or within 12 months from completion of (neo) adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-estrogen or an AI) for metastatic/advanced disease were not included in the study.

- ECOG PS 0 or 1.
- Patients with adequate bone marrow and organ function
- Patients with the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication: sodium, potassium, magnesium, and total calcium (corrected for serum albumin).

Key exclusion criteria

- Symptomatic visceral disease (investigator's judgement).
- Prior chemotherapy (except [neo] adjuvant), fulvestrant, or CDK4/6 inhibitors.
- Prior cumulative of 450 mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin.
- Patients with a known hypersensitivity to any of the excipients of ribociclib or fulvestrant.
- Patients with inflammatory breast cancer at Screening.
- Patients who were concurrently using other anticancer therapy.
- Patients who had major surgery within 14 days prior to starting study drug or had not recovered from major side effects.
- Patients with Child-Pugh score B or C.
- Patients who were currently receiving warfarin or other coumarin-derived anticoagulants, for treatment, prophylaxis, or otherwise. Therapy with heparin, low molecular weight heparin, or fondaparinux was allowed.
- Patients who did not recover from all toxicities related to prior anticancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade ≤ 1. Exception to this criterion: patients with any grade of alopecia were allowed to enter the study.

- Patients who received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who had not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or from whom ≥ 25% of the bone marrow was irradiated.
- Patients with a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell skin carcinoma or curatively resected cervical cancer.
- CNS involvement unless clinically stable without steroids, ≥ 4 weeks from therapy conclusion.
- Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality (long QT syndrome etcetera, refer to CSR for details).

Treatments

Patients were randomly assigned to one of the following treatment arms in a 2:1 ratio:

- Ribociclib (600 mg once daily on Days 1-21 of a 28-day cycle) plus fulvestrant (500 mg in two 5 mL im injections dosed every 28 days on the first day of each cycle with an additional dose on Day 15 of Cycle 1).
- Placebo plus fulvestrant at the above dose.

Study treatment continued until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

Objectives

Primary objective: To compare PFS between ribociclib in combination with fulvestrant to placebo in combination with fulvestrant among men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer who received no or only one prior endocrine treatment (with either antiestrogen or an AI) for advanced disease.

Secondary objectives: To compare the two treatment arms with respect to OS; To evaluate the two treatment arms with respect to overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), and duration of response (DoR); To evaluate the two treatment arms with respect to time to deterioration of Eastern; Cooperative Oncology Group (ECOG) performance status (PS); To evaluate the safety and tolerability of ribociclib in combination with fulvestrant; To evaluate patient-reported outcomes (PROs) for health-related quality of life (HRQoL) in the two treatment arms; To characterize the pharmacokinetics (PK) of ribociclib (and relevant metabolites such as LEQ803) when given in combination with fulvestrant.

Exploratory objectives: To explore exposure/response relationship; To explore potential differences in hospital resource utilization; To assess differences in molecular alterations (main pathways of interest in breast cancer) in patients deriving benefit from treatment; To explore molecular alterations in circulating tumor DNA (ctDNA); To explore potential mechanisms of resistance to treatment with ribociclib plus fulvestrant; To explore potential mechanisms of hepatotoxicity; To explore the long-term benefit intermediate to PFS and OS; by measurement of PFS2.

Outcomes/endpoints

Primary endpoints: PFS

The primary efficacy variable was PFS from Investigator's review of radiology data using RECIST v1.1 criteria. Progression-free survival was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. Discontinuation due to disease progression without supporting objective evidence satisfying progression criteria per RECIST was not considered disease progression for PFS derivation.

The PFS was censored at the last adequate tumor assessment if one of the following occurred: Absence of event, i.e. patients had not progressed or died at the analysis cut-off date; The event occurred after two or more consecutive missing tumor assessments. Discontinuation of study treatment (for any reason) was not considered as a reason for censoring.

Secondary endpoints: Overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), and duration of response (DoR), time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status (PS), safety and tolerability, patient-reported outcomes (PROs) for health-related quality of life (HRQoL), pharmacokinetics (PK).

Patient-reported outcomes were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)–C30 (version 3.0) along with the EuroQoL 5-level instrument (EQ-5D-5L, Version 4.0) and BPI-SF to explore impacts on HRQoL, functioning, disease symptoms, and treatment-related side effects. These questionnaires were administered before any study treatment administrations. All questionnaires were administered in the patient's local language to avoid biasing the patient's perspective. A patient's refusal to complete study questionnaires was not a protocol deviation.

Exploratory endpoints included: exposure/response, hospital resource utilization, molecular alterations in patients deriving benefit (including ctDNA), mechanisms of resistance, mechanism of hepatotoxicity, PFS2.

Sample size

The median time to progression (TTP) for fulvestrant in first-line postmenopausal advanced breast cancer patients is estimated to be between 8 months[13] and 23 months[14]. For the sample size calculation, the median PFS for firstline patients was therefore assumed to be 18 months. For sample size calculation, it was assumed that the median PFS was 6.5 months for fulvestrant as second-line therapy based on CONFIRM trial[15].

Of the patients recruited to the current study, it was anticipated that 40% would be first-line and 60% second-line. The overall median PFS was estimated to be approximately 9 months based on simulation. It was hypothesized that the addition of ribociclib would result in a clinically meaningful 33% reduction in the hazard rate of PFS, corresponding to an increase in median PFS to 13.4 months. A maximum of 364 PFS events was required to detect a hazard ratio of 0.67 with 95% power using the log-rank test at a one-sided cumulative 2.5% level of significance. Assuming that enrollment would continue for approximately 19 months at a uniform rate and there would be a 10% dropout rate by the time of the PFS final analysis, 660 patients needed to be randomized to the two treatment arms in a 2:1 ratio to observe 364 events at approximately 7 months following the randomization of the last patient, i.e. 26 months from the randomization date of the first patient in this study.

[13] Howell et al 2004
[14] FIRST trial; Robertson et al 2012
[15] Di Leo et al 2010

Based on the estimated median PFS and proportion of patients receiving first-line and second line therapy, respectively, it was expected that the accumulation of events in first-line patients would be slower than in second-line patients. To ensure sufficient information was forthcoming from first-line patients, the final analysis was planned to be conducted once approximately 125 events occurred in first-line patients or approximately 364 events occurred in both arms whichever came later.

Overall survival was to be compared between the two treatment arms provided that the primary endpoint, PFS, was statistically significant. Estimates of median OS for fulvestrant alone in the first-line setting were not available. Based on the available date from letrozole monotherapy[16] and anastrozole monotherapy[17], and from data for fulvestrant in relapsed patients with postmenopausal advanced breast cancer[18,19], the median OS for the control arm was estimated via simulation to be approximately 30 months.

It was hypothesized that adding ribociclib to fulvestrant would result in a 29% reduction in the hazard rate for OS (corresponding to an increase in median survival to 42 months). To detect a hazard ratio of 0.71 with 85% cumulative power, a maximum of 351 deaths needed to be observed (using a log-rank test and a 3-look [superiority only] group sequential design at a one sided cumulative 2.5% level of significance).

Randomisation

The randomization ratio was 2:1 (ribociclib plus fulvestrant versus placebo plus fulvestrant) and the randomization was stratified by the presence of liver and/or lung metastases (yes versus no) and previous endocrine therapy.

Blinding (masking)

This was a double blind study.

Statistical methods

Analysis set

The Full Analysis Set (FAS population) consisted of all randomized patients. Following the intent-to-treat principle, patient data were analysed according to the treatment and stratum they were assigned to at randomization.

The Safety Set consisted of all patients who received at least one dose of the study treatment and who had at least one post-baseline safety assessment. Patient data were analyzed according to the treatment actually received. If a patient took at least one dose of the treatment to which he/she was randomized to, then the treatment actually received was the randomized treatment. The statement that a patient had no AE constituted a safety assessment. Occurrence of a death constituted a safety assessment as well.

The Per-protocol Set (PPS) included a subset of the patients from the FAS without major protocol deviations and who took at least one dose of study treatment.

The Pharmacokinetic Analysis Set (PAS) included all patients who provided at least one evaluable PK concentration.

Efficacy analysis

Primary endpoint PFS

[16] Mouridsen et al 2003
[17] Bergh et al 2012
[18] Johnston et al 2013
[19] Di Leo et al 2014

No interim analysis was planned for PFS.

To achieve 95% power for a log-rank test at one-sided 2.5% level of significance, the primary endpoint PFS was to be assessed after approximately 364 PFS events (55% event rate). Analysis also required 125 events in the first line patients. Six hundred and sixty (660) patients were planned to allow 364 events at approximately 7 months following the randomization of the last patient.

The primary efficacy analysis was the comparison of the distribution of PFS between the two treatment arms using a stratified log-rank test (stratum using IRT data) at a one-sided 2.5% level of significance. The PFS survival distribution was estimated using Kaplan-Meier methodology. The PFS hazard ratio with two-sided 95% confidence interval (CI) was derived from the stratified Cox proportional hazards model (stratum using IRT data).

Secondary endpoint OS

A hierarchical testing procedure was adopted in this study and the OS analyses were to be performed only if the primary efficacy endpoint PFS was statistically significant.

A maximum of 3 analyses were planned for OS: at the time of the analysis for PFS (provided PFS was significant), at which point a total 161 deaths (25% event rate) were expected, after 263 events (40% event rate) could be documented, and a final analysis for OS when 351 deaths (53% event rate) were expected (expected 56 months from date of first patient to be randomized). OS tests were carried out using a Lan-Demets (O'Brien-Fleming) alpha spending function.

Table 48: Timelines for interim and final analyses - Study F2301

Months after randomization of the first patient	PFS events	Cumulative Power (%) against a hazard ratio of 0.67	OS events	Cumulative Conditional Power (%) against hazard ratio of 0.71
26	364 (100%)	95	161(46%)	14
39	--	--	263(75%)	60
56	--	--	351(100%)	85

Blinded independent review (BIRC) in audit sample

PFS assessed by Blinded Independent Review Committee (BIRC) was used as a supportive analysis of the primary endpoint.

Based on the audit size calculation approach proposed by Dodd et al (2011), assuming investigator and BIRC assessments are similar and the estimated log of investigator-based HR was -0.40 (i.e. HR=0.67), the audit size of 40% ensured that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio had 86% probability of being below zero (i.e. HR < 1) if the correlation between investigator assessment and BIRC assessment was 0.7 (the estimated correlation based on data from the BELLE-2 [CBKM120F2302] study in metastatic breast cancer).

The following thresholds based on the NCI (Dodd et al 2011) and PhRMA (Amit et al 2011) methods were used to define the trigger for a full BIRC review:

- If the upper-bound of the one-sided 95% confidence interval for BIRC-based log-hazard ratio exceeded zero (i.e. HR>1) based on the NCI method

and/or

- If ≥15% differential discordance was observed in early discordance rate (EDR) or late discordance rate (LDR) according to Amit et al 2011.

Results

Participant flow

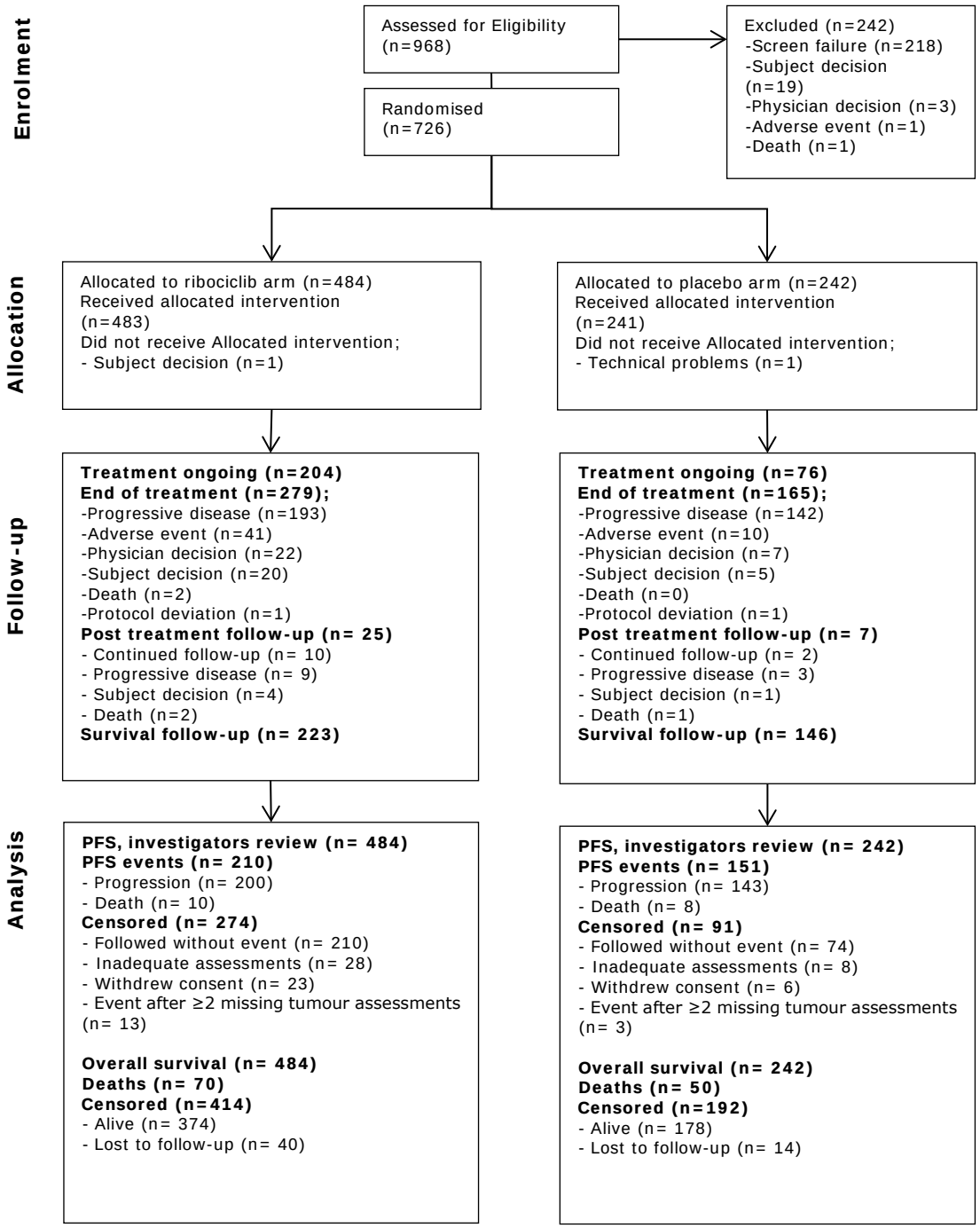


Figure 24: Participant flow - Study F2301

Table 49: Patient disposition (FAS) - Study F2301

Disposition Reason	Ribociclib + Fulvestrant N = 484 n (%)	Placebo + Fulvestrant N = 242 n (%)	All Patients N = 726 n (%)
Patients randomized			
Untreated	1 (0.2)	1 (0.4)	2 (0.3)
Treated	483 (99.8)	241 (99.6)	724 (99.7)
Patients treated			
Treatment ongoing [1]	204 (42.1)	76 (31.4)	280 (38.6)
End of treatment	279 (57.6)	165 (68.2)	444 (61.2)
Reason for end of treatment			
Progressive disease	193 (39.9)	142 (58.7)	335 (46.1)
Adverse event	41 (8.5)	10 (4.1)	51 (7.0)
Physician decision	22 (4.5)	7 (2.9)	29 (4.0)
Subject/guardian decision	21 (4.3)	5 (2.1)	26 (3.6)
Death	2 (0.4)	0	2 (0.3)
Protocol deviation	1 (0.2)	1 (0.4)	2 (0.3)
Technical problems	0	1 (0.4)	1 (0.1)
Entered post-treatment efficacy follow-up [2]	25 (9.0)	7 (4.2)	32 (7.2)
No longer being followed in post-treatment follow-up	15 (5.4)	5 (3.0)	20 (4.5)
Continue to be followed in post-treatment follow-up	10 (3.6)	2 (1.2)	12 (2.7)
Reason for end of post-treatment follow-up [3]	15 (60.0)	5 (71.4)	20 (62.5)
Progressive disease	9 (36.0)	3 (42.9)	12 (37.5)
Subject/guardian decision	4 (16.0)	1 (14.3)	5 (15.6)
Death	2 (8.0)	1 (14.3)	3 (9.4)
Entered survival follow-up [2]	223 (79.9)	146 (88.5)	369 (83.1)

[1] Patients continue study treatment at the time of the cut-off 3-Nov-2017.
[2] The percentages of patients who entered post-treatment follow-up and the percentage of patients who entered survival follow-up use the number of patients with end of treatment as the denominator.
[3] Patients who enter and then discontinue from the post-treatment follow-up phase. In this section the denominator is equal to the number of patients who entered post-treatment follow-up.

Recruitment

First patient enrolled: 09-Jun-2015 (first patient first visit)

Last patient completed: Study ongoing

Data cut-off date for interim analysis: 03-Nov-2017.

Seven-hundred and twenty-six (726) patients were randomized in a ratio of 2:1 with 484 patients in the ribociclib plus fulvestrant arm and 242 patients in the placebo plus fulvestrant arm.

175 sites across 30 countries enrolled patients, the country and respective no. of sites were as follows: Australia (4), Austria (3), Belgium (6), Bulgaria (3), Canada (12), Colombia (2), Czech Republic (5), Denmark (6), France (14), Germany (26), Hungary (5), Italy (8), Jordan(1), Republic of Korea (3), Lebanon (2), Malaysia (2), Mexico (1), Netherlands (12), Norway (1), Poland (2), Portugal (2), Russian federation

(2), Singapore (1), Spain (12), Sweden (3), Switzerland (3), Thailand (2), Turkey (4), United Kingdom (2), United States (26).

Conduct of the study

Protocol amendments

Amendment (Date)	Patients enrolled	Selected changes
1 (17-Feb-2016)	351	Modification of the study population and eligibility criteria to include men (based on Health Authority interactions).
2 (28-Jul-2016)	727	Originally planned futility interim analysis (IA) was eliminated. Originally planned efficacy IA was eliminated and a requirement for a minimum amount of events coming from 1st line patients in the final analysis was added. PFS based on BIRC assessments was not a secondary endpoint but was added as a supportive analysis for the primary analysis. Progression on next-line therapy was added as an exploratory objective.

Protocol deviations

The numbers of major protocol deviations leading to exclusion from the Per-protocol Set were low with no imbalance between the treatment arms. A total of 16 patients (2.2%) were excluded from the Per-protocol Set due to protocol deviations; all deviations were due to the selection criteria not being met and the most frequent one was the criterion for measurable disease or lytic bone lesion not met.

Table 50: Protocol deviations leading to exclusion from the Per-protocol Set (FAS) - Study F2301

	Ribociclib + Fulvestrant N=484	Placebo + Fulvestrant N=242	All Patients N=726
Protocol deviation	**n (%)**	**n (%)**	**n (%)**
Any protocol deviation	11 (2.3)	5 (2.1)	16 (2.2)
Selection criteria not met	11 (2.3)	5 (2.1)	16 (2.2)
Criteria for measurable disease or lytic bone lesion not met	7 (1.4)	3 (1.2)	10 (1.4)
Postmenopausal status not met	4 (0.8)	1 (0.4)	5 (0.7)
Breast cancer type (HR status) not met	0	1 (0.4)	1 (0.1)

A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category.
Patients may have protocol deviations in more than one protocol deviation category..

Baseline data

Table 51: Demographic and baseline characteristics (FAS), Study F2301

Demographic variable	Ribociclib + Fulvestrant N=484	Placebo + Fulvestrant N=242	All Patients N=726
Age (years)			
Mean (standard deviation)	63.4 (9.78)	62.8 (10.59)	63.2 (10.05)
Median	63.0	63.0	63.0
Min, Max	31, 89	34, 86	31, 89
Age category 1 (years) – n (%)			
<65	258 (53.3)	129 (53.3)	387 (53.3)
≥ 65	226 (46.7)	113 (46.7)	339 (46.7)
Age category 2 (years) – n (%)			
<75	419 (86.6)	207 (85.5)	626 (86.2)
≥ 75	65 (13.4)	35 (14.5)	100 (13.8)
Gender – n (%)			
Female	484 (100)	242 (100)	726 (100)
Race – n (%)			
Caucasian	406 (83.9)	213 (88.0)	619 (85.3)
Asian	45 (9.3)	18 (7.4)	63 (8.7)
Native American	5 (1.0)	1 (0.4)	6 (0.8)
Black	3 (0.6)	2 (0.8)	5 (0.7)
Other	10 (2.1)	3 (1.2)	13 (1.8)
Unknown	15 (3.1)	5 (2.1)	20 (2.8)
Region - n (%)			
Europe and Australia	347 (71.7)	173 (71.5)	520 (71.6)
North America	69 (14.3)	43 (17.8)	112 (15.4)
Asia	40 (8.3)	16 (6.6)	56 (7.7)
Latin America	6 (1.2)	3 (1.2)	9 (1.2)
Other	22 (4.5)	7 (2.9)	29 (4.0)
Body mass index (kg/m^2)			
n	474	231	705
Mean (standard deviation)	27.03 (5.487)	27.55 (6.111)	27.20 (5.700)
Median	26.30	26.30	26.30
Min-Max	16.1 -49.0	15.8 – 49.4	15.8 - 49.4
ECOG performance status – n (%)			
0	310 (64.0)	158 (65.3)	468 (64.5)
1	173 (35.7)	83 (34.3)	256 (35.3)
Missing	1 (0.2)	1 (0.4)	2 (0.3)

Approximately 60% of patients had visceral involvement and approximately 21% had bone metastases only. Ninety-nine percent of patients were stage IV at study entry, about 26% had been stage IV at initial diagnosis.

Table 52: Disease history - Study F2301

Disease history	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	All Patients N=726 n (%)
Primary site of cancer - n (%)			
Breast	484 (100.0)	241 (99.6)	725 (99.9)
Missing	0	1 (0.4)	1 (0.1)
Histological grade - n (%)			
Well differentiated	45 (9.3)	30 (12.4)	75 (10.3)
Moderately differentiated	244 (50.4)	123 (50.8)	367 (50.6)
Poorly differentiated	107 (22.1)	53 (21.9)	160 (22.0)
Undifferentiated	9 (1.9)	4 (1.7)	13 (1.8)
Unknown	79 (16.3)	31 (12.8)	110 (15.2)
Missing	0	1 (0.4)	1 (0.1)
Stage at initial diagnosis - n (%)			
0	1 (0.2)	2 (0.8)	3 (0.4)
I	73 (15.1)	43 (17.8)	116 (16.0)
II	167 (34.5)	78 (32.2)	245 (33.7)
III	106 (21.9)	52 (21.5)	158 (21.8)
IV	132 (27.3)	58 (24.0)	190 (26.2)
Unknown	5 (1.0)	7 (2.9)	12 (1.7)
Missing	0	2 (0.8)	2 (0.3)
Stage at time of study entry - n (%)			
II	2 (0.4)	0	2 (0.3)
III	4 (0.8)	2 (0.8)	6 (0.8)
IV	478 (98.8)	239 (98.8)	717 (98.8)
Missing	0	1 (0.4)	1 (0.1)
Disease-free interval - n (%) [1]			
De novo	97 (20.0)	42 (17.4)	139 (19.1)
Non de novo	387 (80.0)	199 (82.2)	586 (80.7)
≤ 12 months	22 (4.5)	9 (3.7)	31 (4.3)
>12 months	365 (75.4)	190 (78.5)	555 (76.4)
Missing	0	1 (0.4)	1 (0.1)
Time since initial diagnosis of primary site (months) - n (%)			
≤ 3 months	82 (16.9)	38 (15.7)	120 (16.5)
>3 and ≤ 12 months	26 (5.4)	11 (4.5)	37 (5.1)
> 12 months	376 (77.7)	192 (79.3)	568 (78.2)
Unknown	0	1 (0.4)	1 (0.1)
Time since initial diagnosis of primary site (months)			
n	484	241	725
Mean	83.67	94.82	87.38
SD	80.424	85.258	82.172
Median	63.64	71.72	66.83

Minimum, Maximum	0.4, 396.5	0.6, 364.3	0.4, 396.5
Time from initial diagnosis to first occurrence/progression (in months)			
n	392	205	597
Mean	89.61	97.76	92.41
SD	70.291	73.583	71.482
Median	75.65	85.36	78.13
Minimum, Maximum	0, 368.7	0, 363.9	0, 368.7
Prior endocrine treatment status - n (%)			
No prior ET [2]	138 (28.5)	74 (30.6)	212 (29.2)
Prior ET	346 (71.5)	167 (69.0)	513 (70.7)
First line patients	236 (48.8)	127 (52.5)	363 (50.0)
Progression on or within 12 months of end of (neo-)adjuvant ET[3]	138 (28.5)	72 (29.8)	210 (28.9)
Progression >12 months of end of (neo-)adjuvant ET	98 (20.2)	55 (22.7)	153 (21.1)
Second line patients[4]	110 (22.7)	40 (16.5)	150 (20.7)
Missing	0	1 (0.4)	1 (0.1)
HER2 receptor status -n (%)			
Negative	484 (100.0)	241 (99.6)	725 (99.9)
Missing	0	1 (0.4)	1 (0.1)
Estrogen receptor status -n (%)			
Positive	481 (99.4)	241 (99.6)	722 (99.4)
Negative	3 (0.6)	0	3 (0.4)
Missing	0	1 (0.4)	1 (0.1)
Progesterone receptor status -n (%)			
Positive	353 (72.9)	167 (69.0)	520 (71.6)
Negative	113 (23.3)	69 (28.5)	182 (25.1)
Unknown	18 (3.7)	5 (2.1)	23 (3.2)
Missing	0	1 (0.4)	1 (0.1)
Estrogen/progesterone receptor status -n (%)			
At least one positive	484 (100.0)	241 (99.6)	725 (99.9)
Both positive	350 (72.3)	167 (69.0)	517 (71.2)
ER positive / PR negative	113 (23.3)	69 (28.5)	182 (25.1)
ER negative / PR positive	3 (0.6)	0	3 (0.4)
ER positive/ PR unknown	18 (3.7)	5 (2.1)	23 (3.2)
Both negative	0	0	0
Other (one negative and one unknown)	0	0	0
Missing	0	1 (0.4)	1 (0.1)
Types of lesions at baseline-n (%)			

Both target and non-target	327 (67.6)	158 (65.3)	485 (66.8)
Non-target only	105 (21.7)	60 (24.8)	165 (22.7)
Target only	52 (10.7)	23 (9.5)	75 (10.3)
Unknown	0	1 (0.4)	1 (0.1)
Current extent of disease (metastatic sites) - n (%)			
Bone	367 (75.8)	180 (74.4)	547 (75.3)
Bone only	103 (21.3)	51 (21.1)	154 (21.2)
Visceral	293 (60.5)	146 (60.3)	439 (60.5)
Lung or liver	242 (50.0)	121 (50.0)	363 (50.0)
Lung	146 (30.2)	72 (29.8)	218 (30.0)
Liver	134 (27.7)	63 (26.0)	197 (27.1)
CNS	6 (1.2)	2 (0.8)	8 (1.1)
Other[5]	102 (21.1)	51 (21.1)	153 (21.1)
Lymph nodes	199 (41.1)	115 (47.5)	314 (43.3)
Soft tissue	23 (4.8)	14 (5.8)	37 (5.1)
Skin	20 (4.1)	8 (3.3)	28 (3.9)
Breast	4 (0.8)	1 (0.4)	5 (0.7)
None	2 (0.4)	0	2 (0.3)
Missing	0	1 (0.4)	1 (0.1)
Number of metastatic sites – n (%)			
0	2 (0.4)	0	2 (0.3)
1	151 (31.2)	73 (30.2)	224 (30.9)
2	156 (32.2)	76 (31.4)	232 (32.0)
3	114 (23.6)	48 (19.8)	162 (22.3)
4	38 (7.9)	34 (14.0)	72 (9.9)
≥ 5	23 (4.8)	10 (4.1)	33 (4.5)
Missing	0	1 (0.4)	1 (0.1)

[1] De novo includes patients with no first recurrence/progression or recurrence/progression within 90 days of diagnosis with no prior antineoplastic medication. For non-de novo patients, DFI is the time from initial diagnosis to first recurrence/progression.
[2] No prior ET (endocrine therapy) include a. de novo patients and b. patients diagnosed with early stages of disease, treated with surgery and/ or RT and/ or chemotherapy (but no endocrine therapy) for that early setting and relapsed afterwards with advanced disease.
[3]1 patient from placebo arm was included in progression on/within 12 months of end of ET but did not have documented ET end date.

[4] 3 patients from ribociclib arm were included in second line but did not have documented disease progression
[5] Other visceral includes any metastatic site other than soft tissue, breast, bone, lung, liver, CNS, skin, and lymph nodes.

Table 53: Prior antineoplastic therapy (FAS) (abbreviated) - Study F2301

Characteristic	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	All Patients N=726 n (%)
Medication: chemotherapy setting [1]			
Adjuvant	209 (43.2)	101 (41.7)	310 (42.7)
Neoadjuvant	65 (13.4)	30 (12.4)	95 (13.1)
Therapeutic	3 (0.6)	0	3 (0.4)
Palliative	1 (0.2)	0	1 (0.1)
Medication: hormonal therapy setting [1]			
Adjuvant	286 (59.1)	139 (57.4)	425 (58.5)
Neoadjuvant	4 (0.8)	6 (2.5)	10 (1.4)
Therapeutic	97 (20.0)	36 (14.9)	133 (18.3)
Palliative	13 (2.7)	4 (1.7)	17 (2.3)

Numbers analysed

Table 54: Analysis sets - Study F2301

Analysis set	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	All Patients N=726 n (%)
Full Analysis Set	484 (100)	242 (100)	726 (100)
Safety Set	483 (99.8)	241 (99.6)	724 (99.7)
Per-protocol Set	472 (97.5)	236 (97.5)	708 (97.5)
Pharmacokinetic Analysis Set	406 (83.9)	0	406 (55.9)

Outcomes and estimation

Data cut-off: 03-Nov-2017

Primary endpoint: PFS by investigator

Table 55: Analysis of PFS per investigator assessment (FAS) - Study F2301

Category	Ribociclib + Fulvestrant N = 484 n (%)	Placebo + Fulvestrant N = 242 n (%)
Number of events - n (%)	210 (43.4)	151 (62.4)
Progression	200 (41.3)	143 (59.1)
Death [1]	10 (2.1)	8 (3.3)
Number censored - n (%)	274 (56.6)	91 (37.6)
P-value ribociclib + fulvestrant versus placebo + fulvestrant [2]	4.10×10^{-7}	
Hazard ratio (95% CI) ribociclib + fulvestrant versus placebo + fulvestrant [3]	0.593 (0.480, 0.732)	
Percentiles (95% CI)		
25th percentile	8.6 (6.5, 10.8)	3.6 (2.5, 5.5)
Median	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)
75th percentile	NE (NE, NE)	22.2 (21.9, NE)
Kaplan-Meier estimate (95% CI)		
6 months	79.4 (75.4, 82.8)	67.0 (60.6, 72.7)
12 months	67.4 (62.8, 71.6)	51.7 (45.1, 57.9)
18 months	55.5 (50.6, 60.1)	38.4 (31.9, 44.9)
24 months	39.6 (30.4, 48.6)	17.6 (8.3, 29.7)

[1] Death before progression
[2] P-value is obtained from the one-sided stratified log-rank test.
[3] Hazard ratio is obtained from Cox PH model stratified by lung and/or liver metastasis and previous endocrine therapy per IRT
NE: Not estimable.

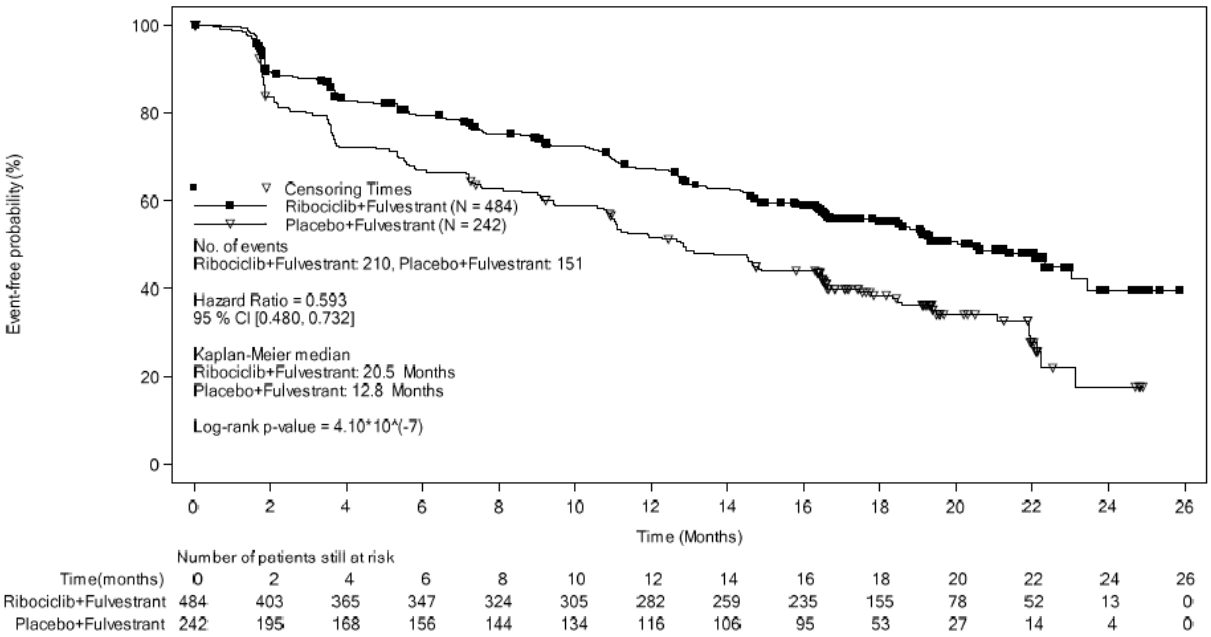


Figure 25: Kaplan-Meier plot of progression-free survival per Investigator assessment (FAS) - Study F2301

Secondary endpoints:

- Overall survival

Table 56: Analysis of OS (FAS) - Study F2301

Category	Ribociclib + Fulvestrant N = 484		Placebo + Fulvestrant N = 242	
Number of events – n (%)	70	(14.5)	50	(20.7)
Number censored – n (%)	414	(85.5)	192	(79.3)
p-value ribociclib versus placebo [1]	0.015			
Hazard ratio (95% confidence interval) [2]	0.670 (0.465, 0.964)			
Percentiles (95% confidence interval)				
25th percentile	NE	(NE, NE)	21.6	(19.8, NE)
Median	NE	(NE, NE)	NE	(NE, NE)
75th percentile	NE	(NE, NE)	NE	(NE, NE)
Kaplan-Meier OS estimate (95% confidence interval)				
12 months	92.1	(89.2, 94.3)	89.3	(84.6, 92.7)
18 months	86.9	(83.4, 89.8)	81.8	(76.1, 86.3)
24 months	80.4	(75.0, 84.8)	72.1	(63.1, 79.2)

[1] P-value was obtained from the one-sided log-rank test stratified by lung and/or liver metastasis, previous endocrine combination partner per IRT. P-value was one-sided and was compared against a threshold of 0.00013 as determined by the Lan-DeMets (O'Brien-Fleming) alpha-spending function for an overall significance level of 0.025.
[2] Hazard ratio was obtained from the Cox PH model stratified by lung and/or liver metastasis, previous endocrine combination partner per IRT.
NE: Not estimable. NR Not reached

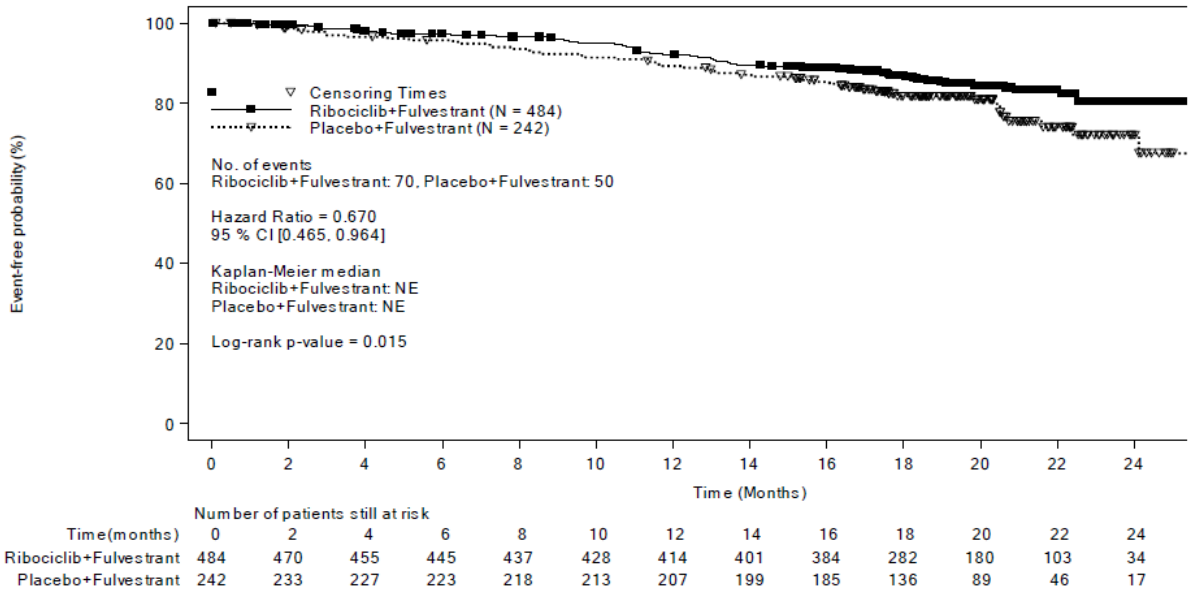


Figure 26: Kaplan-Meier plot of overall survival (FAS) - Study F2301

- Best overall response per investigator assessment

Table 57: Best overall response per Investigator assessment (FAS) - Study F2301

	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	p-value
Best overall response			
Complete response (CR)	8 (1.7)	0	
Partial response (PR)	149 (30.8)	52 (21.5)	
Stable disease (SD)	161 (33.3)	83 (34.3)	
Non-CR/Non-PD	88 (18.2)	54 (22.3)	
Progressive disease (PD)	48 (9.9)	40 (16.5)	
Unknown (UNK)	30 (6.2)	13 (5.4)	
Overall response rate (ORR)	157 (32.4)	52 (21.5)	9.12×10-4
95% CI	(28.3, 36.6)	(16.3, 26.7)	
Clinical benefit rate (CBR)	340 (70.2)	152 (62.8)	0.020
95% CI	(66.2, 74.3)	(56.7, 68.9)	

- Duration of response

Among patients with confirmed CR or PR, the median duration of response was not reached for either arm. The estimated probability of maintaining response for at least 12 months was 78.3% (95% CI: 15.5, 30.0) in the ribociclib plus fulvestrant arm versus 74.8% (95% CI: 15.1, 40.2) in the placebo plus fulvestrant arm.

- Patient reported outcomes

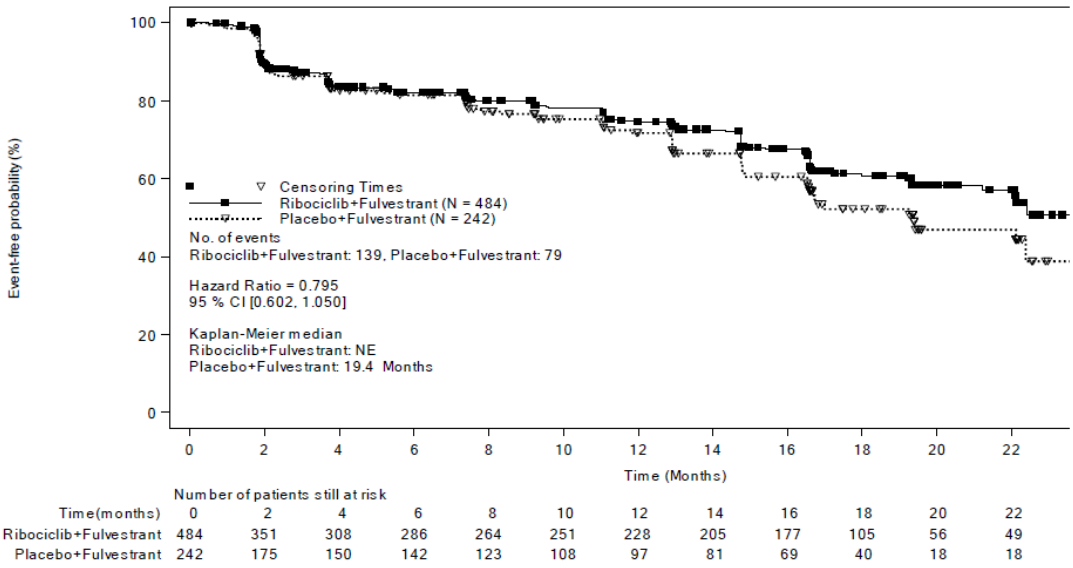


Figure 27: Kaplan-Meier plot of time to definitive deterioration of the global health status/QoL (QL) scale score of the EORTC QLQ-C30 by at least 10% (FAS) - Study F2301

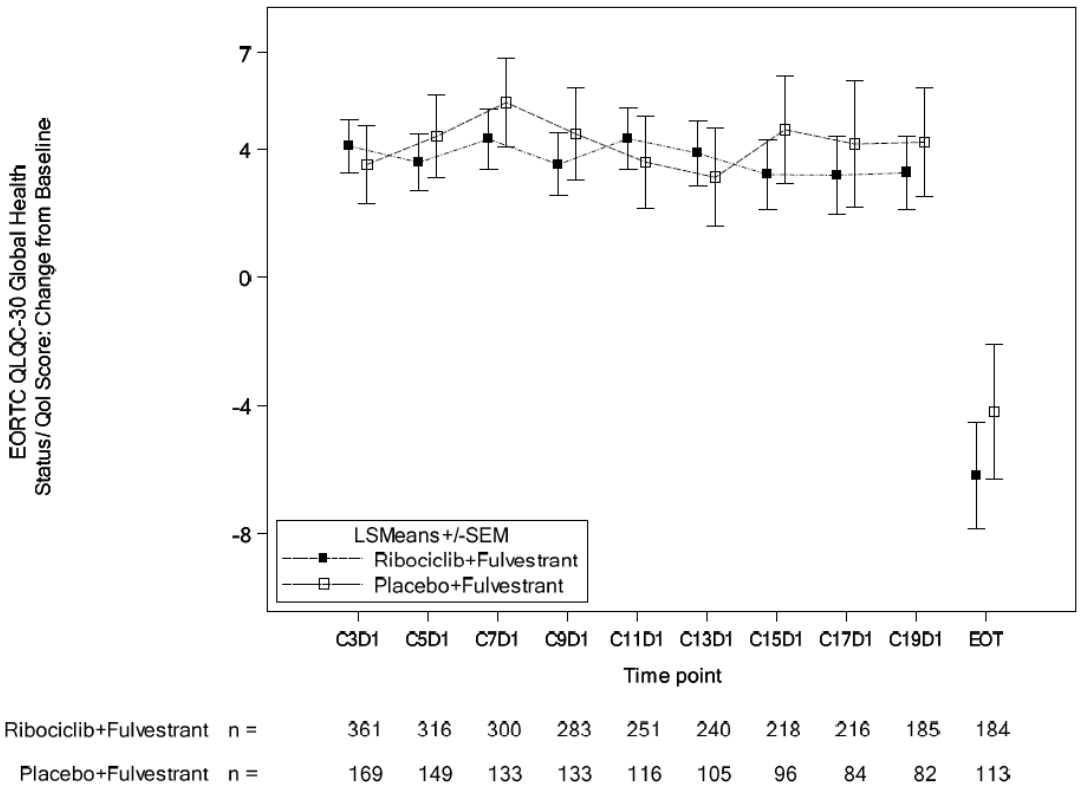


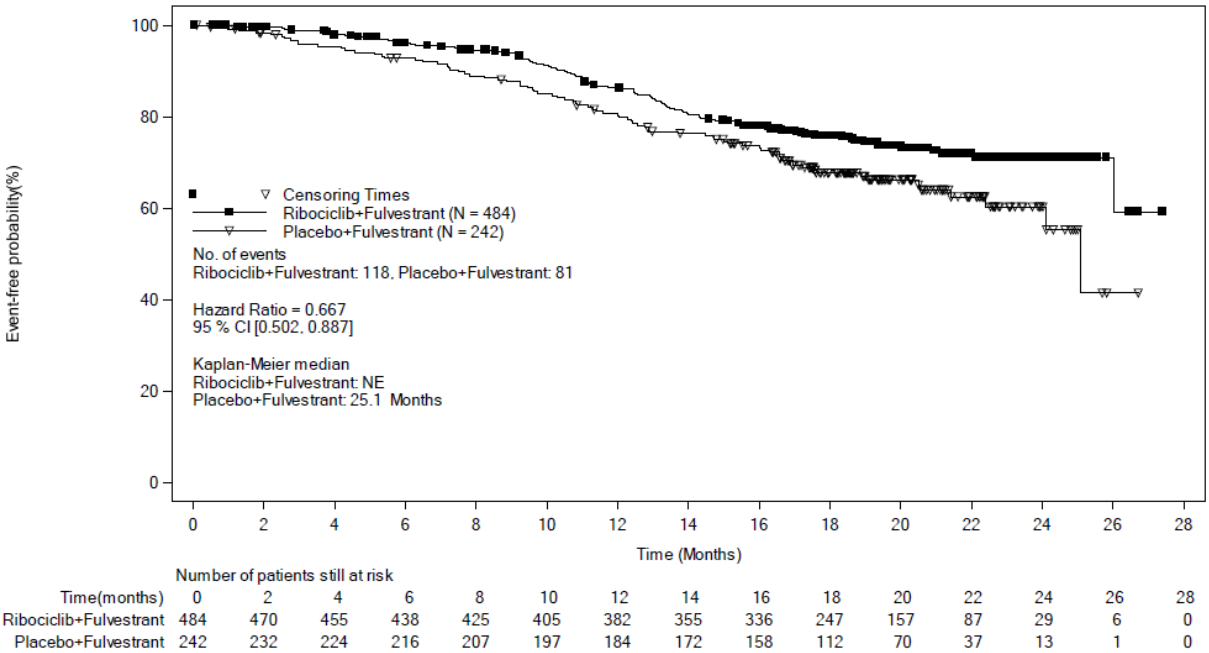
Figure 28: Change from baseline in global health patient-reported outcomes - global health status/QoL scale (QL) score of EORTC QLQ-C30 questionnaire (FAS) - Study F2301

Exploratory endpoints:

- PFS2

Table 58: Stratified Cox regression model for PFS2 (months) based on local investigator's assessment, comparison of treatment with Control Full analysis set - Study F2301

	Events/N (%)	Median Time (95% CI) (months) (1)	Cox model (2) Hazard ratio (3)	95% CI
All Patients				
Placebo+fulvestrant	81/242 (33.5)	25.1 (24.1, NE)		
Ribociclib+fulvestran	118/484 (24.4)	NE (26.0, NE)	0.667	(0.502, 0.887)



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib+Fulvestrant	484	470	455	438	425	405	382	355	336	247	157	87	29	6	0
Placebo+Fulvestrant	242	232	224	216	207	197	184	172	158	112	70	37	13	1	0

Figure 29: Kaplan-Meier plot of PFS2 - Full analysis set - Study F2301

Table 59: Type of events for PFS2 – Full analysis set – Study F2301

	Ribociclib+Fulvestrant N=484 n (%)	Placebo+Fulvestrant N=242 n (%)	All Patients N=726 n (%)
Number of PFS2 events	118 (24.4)	81 (33.5)	199 (27.4)
Progression	68 (14.0)	50 (20.7)	118 (16.3)
Clinical	12 (2.5)	11 (4.5)	23 (3.2)
Radiological	55 (11.4)	39 (16.1)	94 (12.9)
Missing	1 (0.2)	0	1 (0.1)
Death	50 (10.3)	31 (12.8)	81 (11.2)
Death prior to next line therapy	27 (5.6)	19 (7.9)	46 (6.3)
Death on next line therapy	23 (4.8)	12 (5.0)	35 (4.8)
Number censored	366 (75.6)	161 (66.5)	527 (72.6)

Table 60: Reasons for censoring in PFS2 – Full analysis set – Study F2301

Reason of censoring	Ribociclib + Fulvestrant N=484 n(%)	Placebo + Fulvestrant N=242 n(%)	All patients N=726 n(%)
Number of patients censored	366 (75.6)	161 (66.5)	527 (72.6)
Reason of censoring			
Lost to follow-up (1)	40 (8.3)	13 (5.4)	53 (7.3)
No next-line therapy initiated	231 (47.7)	88 (36.4)	319 (43.9)
Next-line therapy initiated with no second next-line therapy	87 (18.0)	56 (23.1)	143 (19.7)
Second next-line therapy initiated	8 (1.7)	4 (1.7)	12 (1.7)

Ancillary analyses

- Sensitivity analyses of PFS per investigator assessment

Table 61: Sensitivity analyses of PFS per Investigator assessment (FAS) - Study F2301

Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)
Primary analysis			
Ribociclib+fulvestrant	20.5(18.5,23.5)	4.10*10^(-7)	0.593(0.480,0.732)
Placebo+fulvestrant	12.8(10.9,16.3)		
Unstratified log-rank test and Cox model			
Ribociclib+fulvestrant	20.5(18.5,23.5)	1.58*10^(-6)	0.611(0.495,0.753)
Placebo+fulvestrant	12.8(10.9,16.3)		
Stratified Cox model, adjusting for baseline covariates [1]			
Ribociclib+fulvestrant	20.5(18.5,23.5)	4.10*10^(-7)	0.580(0.470,0.717)
Placebo+fulvestrant	12.8(10.9,16.3)		
Actual event [2]			
Ribociclib+fulvestrant	19.4(17.6,22.3)	1.04*10^(-6)	0.610(0.496,0.750)
Placebo+fulvestrant	12.8(10.9,14.9)		
Backdating [3]			
Ribociclib+fulvestrant	19.3(16.6,23.0)	1.88*10^(-6)	0.617(0.502,0.759)
Placebo+fulvestrant	12.8(10.9,14.9)		
Censoring for antineoplastic therapy [4]			
Ribociclib+fulvestrant	20.6(18.6,23.5)	1.31*10^(-7)	0.576(0.465,0.713)
Placebo+fulvestrant	12.8(11.0,16.3)		

CI Confidence interval; PFS Progression-free survival
1 Baseline covariates included in the Cox proportional hazard model are age (≥ 65 vs <65), prior chemo therapy in (neo)adjuvant setting (yes vs no), ECOG performance status (0 versus 1), and bone only lesion at baseline (yes or no).
2 Analysis included the event whenever it occurred even after ≥ 2 missing tumor assessments
3 Analysis used the date of the next scheduled assessment for events occurring after >=1 missing assessment
4 Analysis was performed by censoring patients at start of new antineoplastic therapy

- PFS per BIRC review in audit sample

Table 62: Analysis of PFS per BIRC assessment for audited patients (FAS) - Study F2301

Category	Ribociclib + Fulvestrant N = 193 n (%)	Placebo + Fulvestrant N = 97 n (%)
Number of events - n (%)	72 (37.3)	54 (55.7)
Progression	62 (32.1)	52 (53.6)
Death [1]	10 (5.2)	2 (2.1)
Number censored - n (%)	121 (62.7)	43 (44.3)
Hazard ratio (95% CI) ribociclib + fulvestrant versus placebo + fulvestrant [2]	0.492 (0.345, 0.703)	
Percentiles (95% CI)		
25th percentile	9.2 (5.6, 11.0)	2.1 (1.8, 3.6)
Median	NE (18.2, NE)	10.9 (3.8, 17.2)
75th percentile	NE (NE, NE)	22.2 (19.1, 22.2)

[1] Death before progression.
[2] Hazard ratio is obtained from Cox PH model stratified by lung and/or liver metastasis and previous endocrine therapy per IRT
NE: Not estimable.

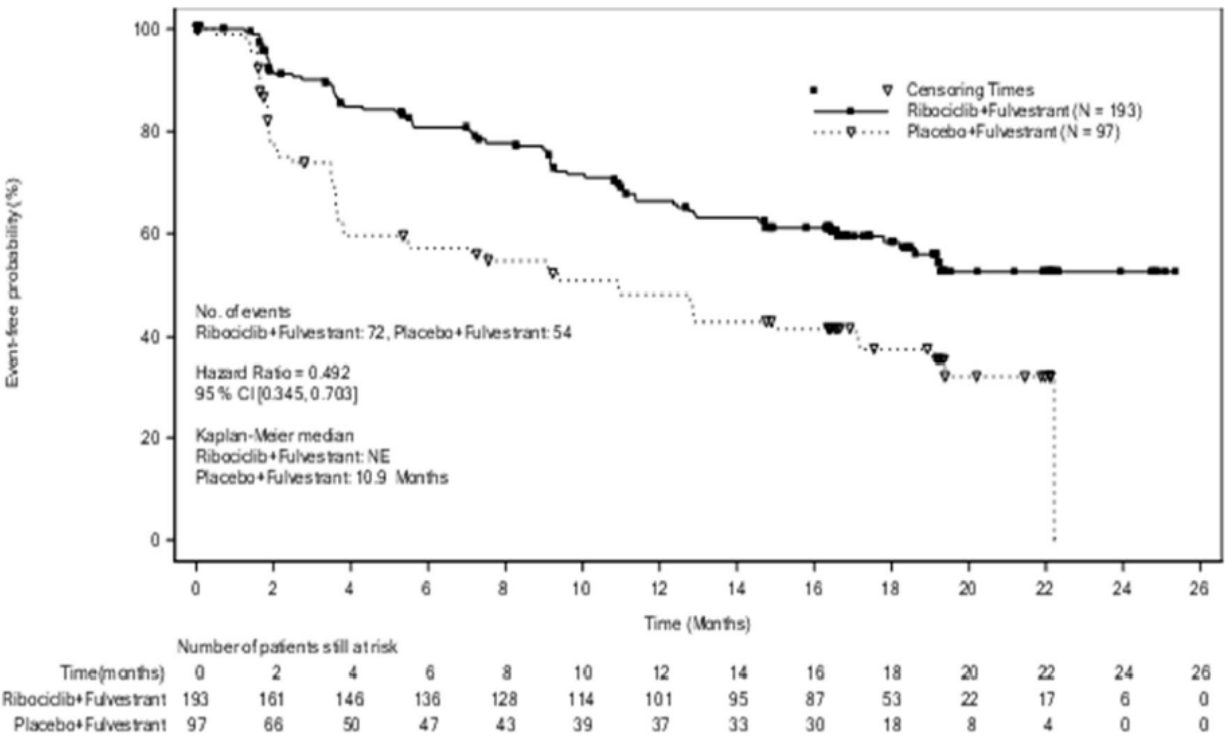


Figure 30: Kaplan-Meier plot of progression-free survival per BIRC assessment for audited subjects (FAS) - Study F2301

- Concordance in PFS by investigator and BIRC

Table 63: Early and late discrepancy rates and differential discordance of progression status per investigator and BIRC Full analysis set - Study F2301

Progression per investigator (INV)	Progression per BIRC	Timing	Ribociclib + Fulvestrant N=193	Placebo + Fulvestrant N=97
PD	PD	Same time (a1)	24	20
PD	PD	INV after BIRC (a2)	26	22
PD	PD	INV before BIRC (a3)	0	1
PD	PD	Total (a)	50	43
PD	No PD	Total (b)	27	13
No PD	PD	Total (c)	12	9
No PD	No PD	Total (d)	104	32
Early discrepancy rate (EDR): (b+a3)/(a+b)			0.351	0.250
Differential discordance of EDR			0.101	
Late discrepancy rate (LDR): (c+a2)/(b+c+a2+a3)			0.585	0.689
Differential discordance of LDR			-0.104	

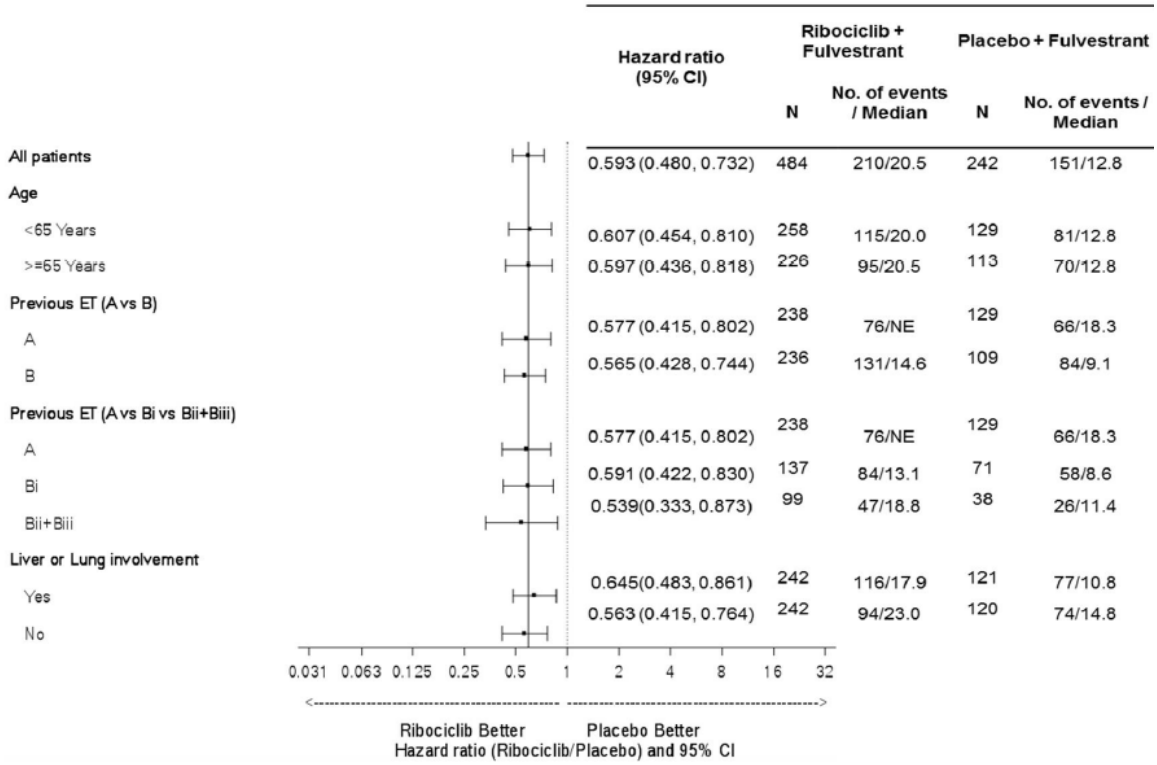
- PFS: Censoring reasons

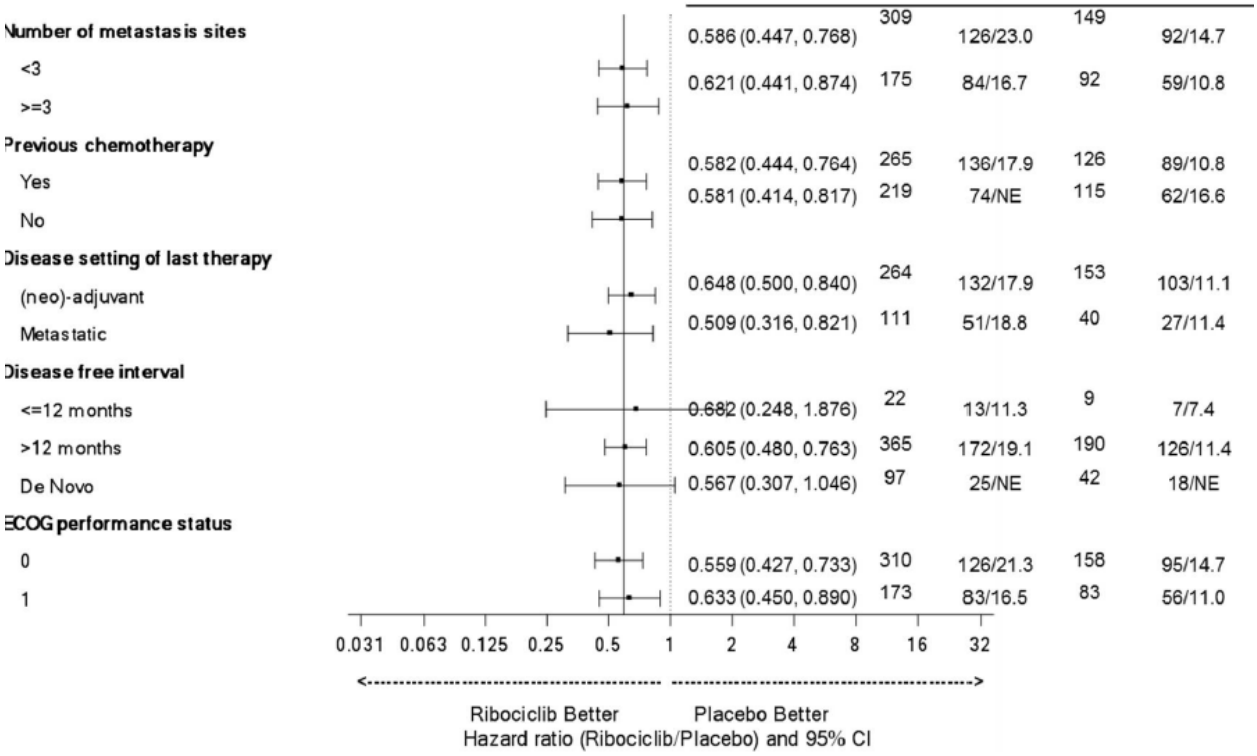
Table 64: PFS censoring reasons per Investigator and BIRC assessment (FAS) - Study F2301

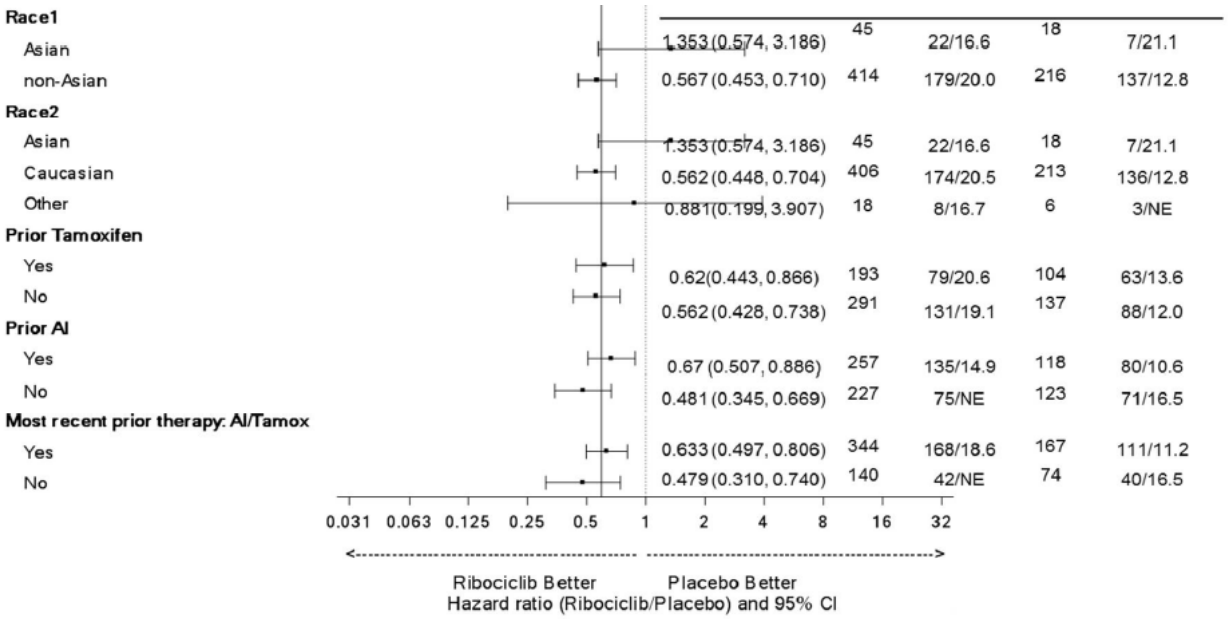
	Investigator assessment		BIRC review	
	Ribociclib + Fulvestrant N=484	Placebo + Fulvestrant N=242	Ribociclib + Fulvestrant N=193*	Placebo + Fulvestrant N=97*
Reason of censoring	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients censored	274 (56.6)	91 (37.6)	121 (62.7)	43 (44.3)
Reason of censoring				
Ongoing without event [1]	210 (43.4)	74 (30.6)	83 (43.0)	25 (25.8)
Lost to follow-up [2]	0	0	0	0
Withdrew consent	23 (4.8)	6 (2.5)	7 (3.6)	3 (3.1)
Event documented after two or more missing tumor assessments	13 (2.7)	3 (1.2)	6 (3.1)	4 (4.1)
Adequate assessment no longer available [3]	28 (5.8)	8 (3.3)	25 (13.0)	11 (11.3)

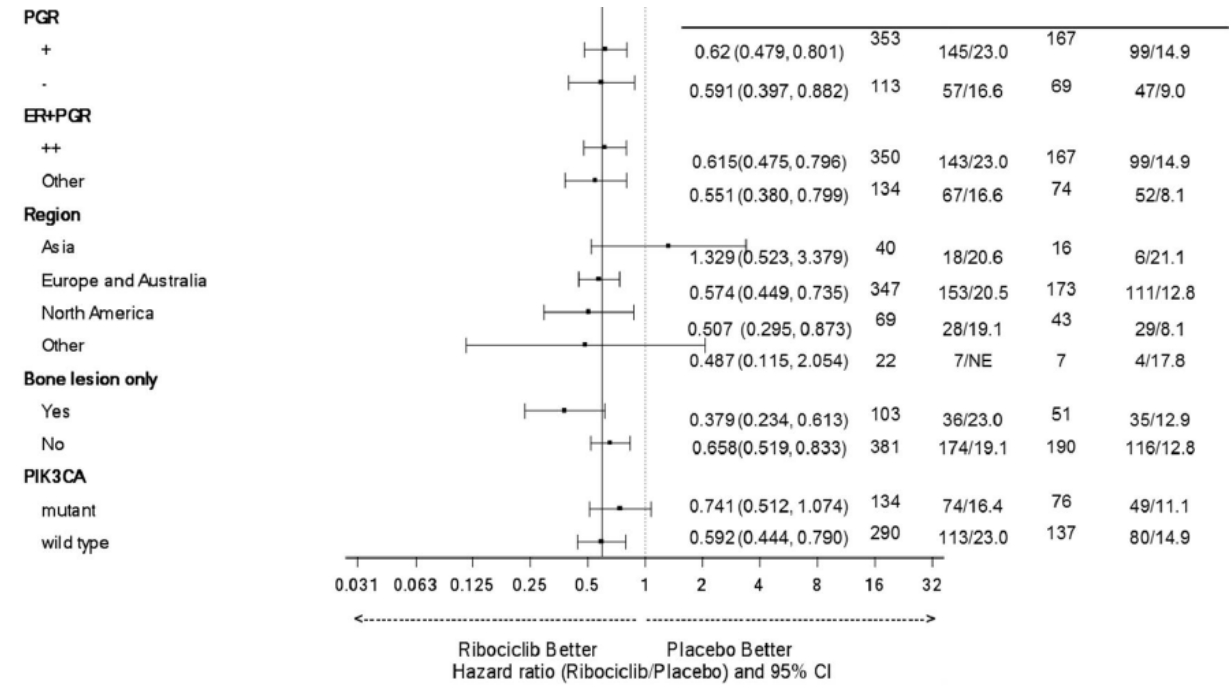
* For BIRC review, N is the number of patients included in the BIRC review.
[1] Patients without event and had adequate follow-up as of data cut-off
[2] Recorded on the End of treatment CRF or Study evaluation completion CRF
[3] Patients censored without adequate evaluations for a specified period prior to data cut-off or without adequate baseline assessment

- PFS in subgroups






Race1
Asian
1.353 (0.574, 3.186) 45 22/16.6 18 7/21.1
non-Asian
0.567 (0.453, 0.710) 414 179/20.0 216 137/12.8
Race2
Asian
1.353 (0.574, 3.186) 45 22/16.6 18 7/21.1
Caucasian
0.562 (0.448, 0.704) 406 174/20.5 213 136/12.8
Other
0.881 (0.199, 3.907) 18 8/16.7 6 3/NE
Prior Tamoxifen
Yes
0.62 (0.443, 0.866) 193 79/20.6 104 63/13.6
No
0.562 (0.428, 0.738) 291 131/19.1 137 88/12.0
Prior AI
Yes
0.67 (0.507, 0.886) 257 135/14.9 118 80/10.6
No
0.481 (0.345, 0.669) 227 75/NE 123 71/16.5
Most recent prior therapy: AI/Tamox
Yes
0.633 (0.497, 0.806) 344 168/18.6 167 111/11.2
No
0.479 (0.310, 0.740) 140 42/NE 74 40/16.5
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


PGR
+
0.62 (0.479, 0.801) 353 145/23.0 167 99/14.9
-
0.591 (0.397, 0.882) 113 57/16.6 69 47/9.0
ER+PGR
++
0.615 (0.475, 0.796) 350 143/23.0 167 99/14.9
Other
0.551 (0.380, 0.799) 134 67/16.6 74 52/8.1
Region
Asia
1.329 (0.523, 3.379) 40 18/20.6 16 6/21.1
Europe and Australia
0.574 (0.449, 0.735) 347 153/20.5 173 111/12.8
North America
0.507 (0.295, 0.873) 69 28/19.1 43 29/8.1
Other
0.487 (0.115, 2.054) 22 7/NE 7 4/17.8
Bone lesion only
Yes
0.379 (0.234, 0.613) 103 36/23.0 51 35/12.9
No
0.658 (0.519, 0.833) 381 174/19.1 190 116/12.8
PIK3CA
mutant
0.741 (0.512, 1.074) 134 74/16.4 76 49/11.1
wild type
0.592 (0.444, 0.790) 290 113/23.0 137 80/14.9
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI

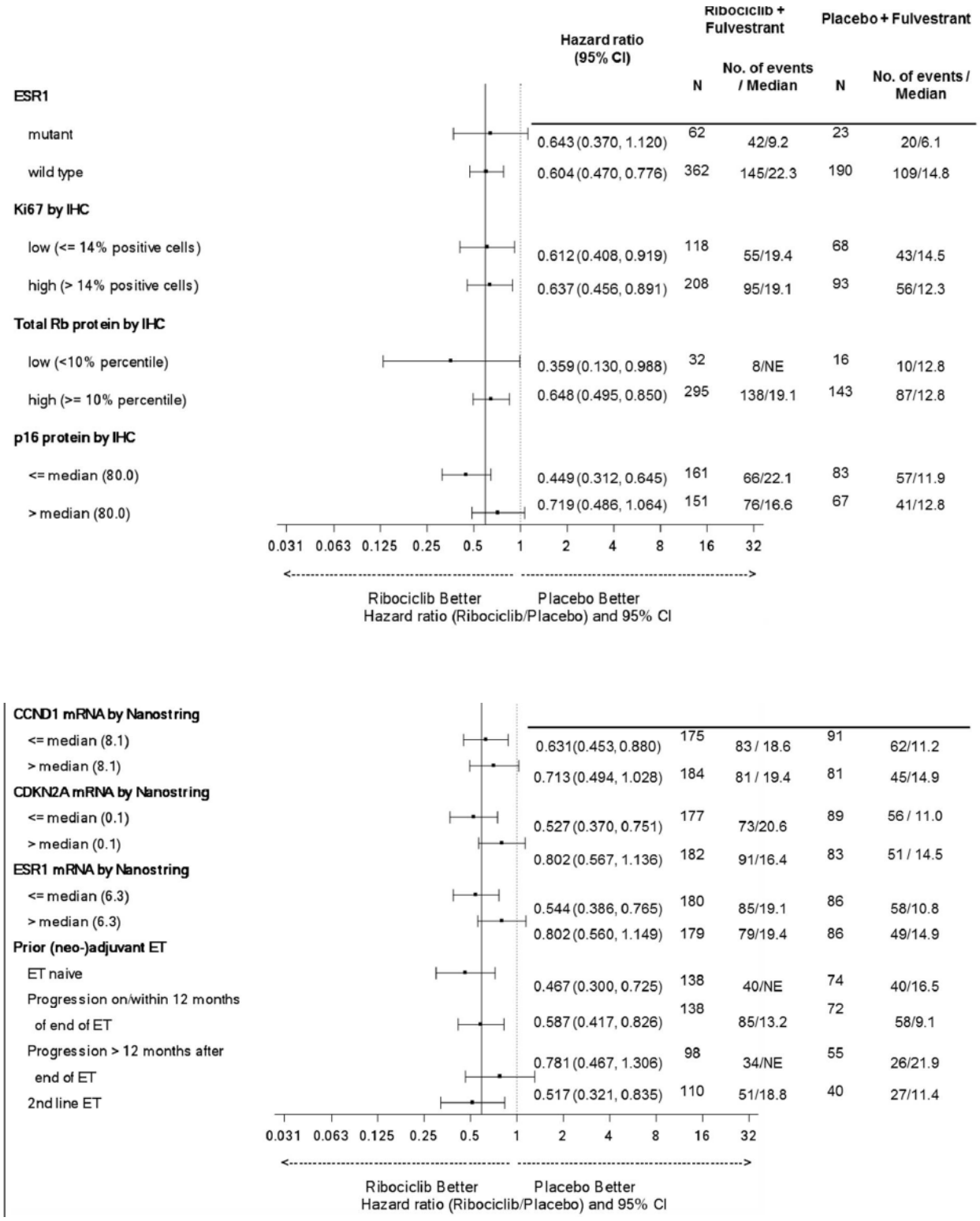


Figure 31: Forest plot of progression-free survival per Investigator assessment from subgroup analysis (FAS) - Study F2301

- Best overall response per BIRC assessment

Table 65: Best overall response per BIRC assessment for audit sample of patients (FAS) - Study F2301

	Ribociclib + Fulvestrant N=193 n (%)	Placebo + Fulvestrant N=97 n (%)
Best overall response		
Complete response (CR)	1 (0.5)	1 (1.0)
Partial response (PR)	52 (26.9)	14 (14.4)
Stable disease (SD)	53 (27.5)	27 (27.8)
Non-CR/Non-PD	59 (30.6)	24 (24.7)
Progressive disease (PD)	15 (7.8)	21 (21.6)
Unknown (UNK)	13 (6.7)	10 (10.3)
Overall response rate (ORR)	53 (27.5)	15 (15.5)
95% CI	(21.2, 33.8)	(8.3, 22.7)
Clinical benefit rate (CBR)	135 (69.9)	47 (48.5)
95% CI	(63.5, 76.4)	(38.5, 58.4)

N is the denominator for percentage calculation.
The 95% CIs for the frequency distribution of each variable were computed using normal approximation
Overall response rate = proportion of patients with CR or PR
Clinical benefit rate = proportion of patients with CR or PR, or SD or Non-CR/Non-PD>24 weeks
Source: Table 14.2-1.24

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial CLEE011E2301 (MONALEESA-7)

<table>
<tr><td colspan="3">Title: A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer</td></tr>
<tr><td>Study identifier</td><td colspan="2">CLEE011E2301 (MONALEESA-7)</td></tr>
<tr><td>Design</td><td colspan="2">A randomized, double blind, placebo-controlled, multicenter, Phase III, global study compared the combination of ribociclib (once daily, on Days 1-21 of a 28-day cycle) plus goserelin (3.6 mg subcutaneously implant on Day 1 of every 28-day cycle) plus either tamoxifen (20 mg orally once daily) or a NSAI (letrozole 2.5 mg or anastrozole 1 mg) to placebo plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole).

Patients were pre- or perimenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior hormonal therapy and were randomly assigned in a 1:1 ratio to either the ribociclib or the placebo arm.

Treatment crossover from placebo to ribociclib was not permitted in this study.</td></tr>
<tr><td></td><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>Not applicable
Not applicable
Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority</td></tr>
<tr><td>Treatments groups</td><td>Investigational arm
335 patients</td><td>Ribociclib 600 mg days 1-21 of each 28-day cycle plus tamoxifen 20 mg QD or a NSAI (letrozole 2.5 mg QD or anastrozole 1 mg QD) plus goserelin 3.6 mg subcutaneously of each 28-day cycle.</td></tr>
</table>

	Control arm 337 patients		Placebo plus tamoxifen or a NSAI (letrozole or anastrozole) plus goserelin.
Endpoints and definitions	Primary endpoint	PFS	Progression-free survival
	Key secondary endpoint	OS	Overall survival
	Secondary endpoints	ORR CBR TTR DOR	Overall response rate Clinical benefit rate Time to response Duration of response time to deterioration of ECOG status health-related quality of life (QoL) safety and tolerability
	Exploratory endpoints	PK, molecular alterations (including ctDNA), mechanisms of resistance, estradiol (E2) suppression, effect of cytochrome P450 (CYP) 2D6 genotype on tamoxifen, work productivity and activity impairment, hospital resource utilization, mechanisms of hepatotoxicity (not analyzed at this cut-off), PFS2.	
Database lock	20-Aug-2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population Final (only) PFS analysis, 20-Aug-2017		
Descriptive statistics and estimate variability	Treatment group	Ribociclib	Placebo
	Number of subject	335	337
	PFS by investigator, months (median)	23.8	13.0
	95% CI of median	19.2 - NE	11.0 – 16.4
	OS, months (median)	NE	29.4
	95% CI of median	NE - NE	28.2 - NE
	ORR, proportion (%)	40.9%	29.7%
	95% CI of proportion	35.6 – 46.2%	24.8 – 34.6%

Effect estimate per comparison	**PFS** by investigator	Comparison groups	Ribocilib vs. placebo
		Hazard ratio (HR)	0.553
		95% CI of HT	0.441 – 0.694
		P-value	9.83×10^{-8}
	OS	Comparison groups	Ribocilib vs. placebo
		Hazard ratio (HR)	0.916
		95% CI of HT	0.601 – 1.396
		P-value	0.34

	ORR	Comparison groups	Ribocilib vs. placebo
		Difference	11.2
		95% CI of difference	4.0 - 18
		P-value	9.80×10^{-4}

Summary of Efficacy for trial CLEE011F2301 (MONALEESA-3)

Title: A randomized double-blind, placebo controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.			
Study identifier	CLEE011F2301 (MONALEESA-3)		
Design	This was an international, multicenter, randomized, double-blind, placebo-controlled two-arm study with the objective to evaluate the efficacy and safety of adding ribociclib (600 mg as three 200 mg capsules once daily on Days 1 to 21 of a 28-day cycle.) to fulvestrant in men and postmenopausal women with advanced breast cancer. Patients who were treatment naive or patients who received up to one line of prior endocrine therapy were included in the study. The randomization ratio was 2:1, stratified by the presence of liver and/or lung metastases (yes versus no) and previous endocrine therapy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Investigational arm 484 patients		Ribociclib 600 mg days 1-21 of each 28-day cycle plus fulvestrant 500 mg in two 5 mL im injections dosed every 28 days on the first day of each cycle with an additional dose on Day 15 of Cycle 1.
	Control arm 242 patients		Placebo plus fulvestrant
Endpoints and definitions	Primary endpoint	PFS	Progression-free survival
	Secondary endpoints	OS ORR CBR TTR DOR	Overall survival Overall response rate Clinical benefit rate Time to response Duration of response time to deterioration of ECOG) status, safety and tolerability, patient-reported outcomes (PROs) for health-related quality of life (HRQoL), pharmacokinetics (PK).
	Exploratory endpoints	Exposure/response, hospital resource utilization, molecular alterations in patients deriving benefit (including ctDNA), mechanisms of resistance, mechanism of hepatotoxicity, PFS2.	
Database lock	03-Nov-2017		
Results and Analysis			

Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat population Final (only) PFS analysis, 03-Nov-2017		
Descriptive statistics and estimate variability	Treatment group	Ribociclib	Placebo
	Number of subject	484	242
	PFS by investigator, months (median)	20.5	12.8
	95% CI of median	18.5 – 23.5	10.9 – 16.3
	OS, months (median)	NE	NE
	95% CI of median	NE - NE	NE - NE
	ORR, proportion (%)	32.4%	21.5%
	95% CI of proportion	28.3 – 36.6%	16.3 – 26.7%

Effect estimate per comparison	**PFS** by investigator	Comparison groups	Ribocilib vs. placebo
		Hazard ratio (HR)	0.593
		95% CI of HT	0.480 – 0.732
		P-value	4.10×10^{-7}
	OS	Comparison groups	Ribocilib vs. placebo
		Hazard ratio (HR)	0.670
		95% CI of HT	0.465 – 0.964
		P-value	0.015
	ORR	Comparison groups	Ribocilib vs. placebo
		Difference	10.9
		95% CI of difference	4.3 - 18
		P-value	9.1×10^{-4}

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

With regards to dose selection, all drugs used in Studies E2301 and F2301 were administered at doses according to their approved SmPCs. Based on current available data, there was a low probability of clinically meaningful DDIs between ribociclib and other study treatments.

Regarding the dose tamoxifen in study E2301, it was expected that the combination of ribociclib (600 mg) with tamoxifen (20 mg daily and goserelin) would be well tolerated, even with the knowledge that there was the potential for an increase in tamoxifen exposure as well as the possibility that tamoxifen increases QT prolongation. NSAI or tamoxifen was investigators choice unless less than 12 months had passed since (neo) adjuvant treatment, in this situation the endocrine backbone was switched (tamoxifen to AI or vice versa).

Selection of the ribociclib dose and regimen (600 mg daily on Days 1 to 21 of a 28-day cycle) was based on results from the first in-human study of single-agent ribociclib Study CLEE011X2101 and was also consistent with the previously approved dosing schedule used in combination with letrozole in the registration Study A2301 in patients with advanced breast cancer. Studies X2101 and A2301 were a part of the initial MAA

submission and are not discussed further here. Additionally, data from an additional 13 patients exposed to the same regimen in Phase Ib X2108 study (Arm 3) were also submitted (data not shown).

The overall design of the randomized, active-controlled studies MONALEESA 7 and MONALEESA 3 is considered acceptable.

Patient populations in the trials, as identified by eligibility criteria, were relevant to the respective 1st line indication of ribociclib as add on to a non-steroidal aromatase inhibitor for pre- and perimenopausal women, and the 1st and 2nd line indication as add-on to fulvestrant in the setting of advanced disease. The chosen comparators are considered appropriate, in line with international guidelines and scientific advice (EMEA/H/SA/2912/1/2014/II).

No patients with critical visceral disease were included in the two pivotal studies. It is adequately reflected in the current SmPC that the efficacy and safety of ribociclib have not been studied in patients with critical visceral disease (see SmPC section 4.4).

In advanced breast cancer, prolonging survival and alleviating disease symptoms are relevant aims of therapy. Although OS is the most persuasive endpoint, PFS is an acceptable primary endpoint. Possible benefits of a PFS gain include delayed symptomatic deterioration, postponed chemotherapy, and extension of life span provided no disease-modifying effects of ribociclib beyond discontinuation. Such an effect has been discussed for CDK 4/6 inhibitors. Therefore, in the absence of mature OS data, PFS2 is considered important supporting evidence, as highlighted in the scientific advice (EMEA/H/SA/2912/1/2014/II).

For both studies, the statistical analysis plan is overall acceptable. Generally, commonly expected methods were used. Pre-specified PFS censoring rules did not include an analysis where initiation of new antineoplastic therapy was considered an event (see discussion under efficacy data and additional analyses).

In both studies, some changes to planned analyses were implemented. The more important changes involved removing interim analyses of PFS, keeping only the final analysis. The changes are deemed not to affect the integrity of key results. Overall, the studies are considered to be well conducted.

Efficacy data and additional analyses

Study MONALEESA 7 (E2301)

With regards to baseline data, NSAI or tamoxifen was chosen at investigators discretion for about 70% of patients with no prior [neo]adjuvant endocrine therapy or progression > 12 months after end of such therapy. In accordance with eligibility criteria that allowed prior chemo- but not endocrine therapy in the advanced setting (unless ≤ 14 days of tamoxifen or NSAI or ≤ 28 days goserelin), 14% of patients had received prior (advanced setting) chemotherapy, whereas 0.6% had received prior (advanced setting) endocrine therapy.

Demographic characteristics were balanced between arms. The average age was 43 years, 58% of patients were Caucasian, Europe and Australia contributed 41% of patients, Asia 27%, North America 14%.

Baseline disease characteristics were balanced between the two arms. About 40% of patients had stage IV disease at baseline (de novo metastatic), 24% had bone-only metastatic disease and 57% visceral metastatic disease. Very few (2) patients had locally advanced (not distant metastatic) disease.

The planned final analysis was conducted when 318 events had occurred (39% and 56% event rate for the ribociclib and placebo arms respectively). The primary study objective was met. The HR of 0.55 is likely a robust estimate of the relative PFS benefit. PFS medians were 23.8 months and 13.0 months for the Kisqali plus NSAI/tamoxifen plus goserelin arm and placebo plus NSAI/tamoxifen plus goserelin arm respectively, and the resulting PFS increase of approximately 11 months is of clinical benefit.

In investigators analysis, PFS events or administrative censorings (ongoing without event) accounted for >90% of patients in both arms, i.e. the loss of informative data points was limited.

Results were consistent in sensitivity analyses with small differences in numbers for 'actual event', 'backdating', and 'censoring for antineoplastic therapy' approaches (131 [placebo] and 187 [ribociclib] in primary analysis, 133 and 191 in 'actual event', 133 and 191 in 'backdating', and 127 and 183 in 'censoring for new anticancer therapy'). An analysis where new anticancer therapy is considered an event was also provided (data not shown) and was consistent with the primary analysis results.

The thresholds for conducting a full BIRC review were not met and BIRC assessment was conducted on a random subset of 40% of patients. The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomised patients were supportive of the primary efficacy results based on the investigator's assessment (hazard ratio of 0.427; 95% CI: 0.288, 0.633). The BIRC analysis indicated a degree of bias in investigators assessment; investigators PDs were not confirmed in 29% and 19% of cases (ribociclib and placebo, respectively), whereas for agreed upon cases, investigators were late compared to BICR in 27% vs 35% of cases. The overall effect of investigators' bias appears to disfavor the ribociclib arm.

With regards to PFS subgroup analysis, the results were consistent between the different subgroups.

The PFS 2 had a low event rate of about 20% and hence, the findings offered limited support (HR 0.84, 95% CI 0.6-1.2). Among censored patients in this analysis, more patients had not yet commenced second-line therapy in the ribociclib arm (61% vs. 47% for placebo).

At the time of the primary PFS analysis overall survival data were not mature with 89 (13%) of deaths (HR 0. 916 [95% CI: 0.601, 1.396]). It is currently unclear what long-term effect on OS is to be expected. Nevertheless, a detrimental OS effect is unlikely given the large treatment-effect on PFS and based on the evaluation of deaths on study and in follow up. The OS findings at final PFS analysis are still immature with an event rate of < 15%. It is currently projected that the 189 deaths for the next OS interim analysis will be reached in approximately 2Q2019 and the 252 deaths for the final analysis will be reached in approximately 4Q2020. The CHMP recommends submitting remaining OS analyses when available.

The ORR data supported the PFS result where ORR per investigator assessment based on RECIST v1.1 was higher in the Kisqali arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6). In the audit sample, the ORR was 45.9% (61/133) for ribociclib vs. 28.4% (38/134) for placebo.

It was noted that NSAI-treated patients had better progression-free survival compared with the tamoxifen group: median PFS was 28 and 14 months for ribociclib+NSAI vs control arms, compared to 22 and 11 for ribociclib+tamoxifen vs control. The MAH noted there were more patients with de novo metastatic disease in the tamoxifen subpopulation relative to the NSAI subpopulation (72% vs. 29%), and higher numbers of patients not having received prior neo-adjuvant/adjuvant endocrine therapy (92% vs. 49%).

Contrary to the longer PFS estimates in the NSAI compared to the tamoxifen subgroups, responses were lower in patients with NSAI as endocrine combination partner, with ORR 39 % and 29% (NSAI, placebo) compared to 46% and 31% for tamoxifen and placebo. As these endocrine treatments (NSAI vs. tamoxifen) are systematically different, the response-to-PFS relationship may be different or it could be a chance finding. Nonetheless, these results do not affect the conclusion on the efficacy outcomes where a clinical benefit was observed with either NSAI or tamoxifen.

Although somewhat hampered by lower numbers, PFS results in subgroups analyses in NSAI patients were consistent between the different groups.

Study MONALEESA 3 (F2301)

Baseline characteristics were balanced between the treatment arms. Although a majority of patients had received prior endocrine therapy, about 21% had received prior endocrine therapy in the advanced setting, i.e. were 2nd line patients.

The applicant stated that due to the rapid enrollment prior to implementation of Amendment 1, no male patients were included.

The planned final analysis was conducted when 361 events had occurred (43% and 62% event rate for the ribociclib and placebo arms respectively). The median follow up time at the time of primary PFS analysis was 20.4 months. The primary study objective was met. The HR of 0.59 is likely a robust estimate of the relative PFS benefit, PFS medians were 20.5 and 12.8 months for the ribociclib and placebo arms respectively, and the resulting PFS increase of approximately 8 months is of clinical benefit.

Results were consistent in sensitivity analyses. An additional analysis where new anticancer therapy was considered an event was provided (data not shown) and showed consistency.

In the subgroup of patients who were treatment naive in the metastatic/advanced disease setting, the hazard ratio was of 0.577 (95% CI: 0.415, 0.802), with a median PFS not reached in the Kisqali arm and 18.3 months (95% CI: 14.8, 23.1) in the placebo arm. In the subgroup of patients who had received up to one line of treatment for metastatic/advanced disease, the hazard ratio was of 0.565 (95% CI: 0.428, 0.744), with a median PFS of 14.6 months (95% CI: 12.5, 18.5) and 9.1 months (95% CI: 6.1, 11.1) in the Kisqali and placebo arms, respectively. Within this subgroup, the hazard ratio for the second line patients who had received prior endocrine therapy in the advanced breast cancer setting was 0.539 (95% CI: 0.333, 0.873), with a median PFS of 18.8 months (95% CI: 12.5, NE) and 11.4 months (95% CI: 3.7, 16.3) in the Kisqali and placebo arms, respectively.

As for MONALEESA 7, the BIRC analysis indicated a degree of bias in investigators assessment; investigators PDs were not confirmed in 35% and 23% of cases (ribociclib and placebo, respectively), whereas for agreed upon cases, investigators were late compared to BICR in 34% vs 39% of cases. The pattern was similar in the two studies, and the overall effect of investigators' bias appeared to disfavor the ribociclib arm.

In investigators analysis, PFS events or administrative censorings (ongoing without event) accounted for 87% and 93% of patients in the experimental and control arms respectively, i.e. the loss of informative data points was limited.

With regards to PFS in subgroup, the interpretation of findings in the Asian subpopulation is very uncertain due to low numbers. Otherwise, no concerning inconsistencies were found. In the ~21% of patients that had received previous endocrine therapy in the advanced setting ("2nd line ET"; relevant to the sought indication), the HR was 0.52 (0.32 – 0.84). In this study, 46.7% of patients were of age 65 years and older, including 13.8% patients of age 75 years and older. No overall differences in efficacy of Kisqali were observed between these patients and younger patients (see SmPC section 4.2 and 5.1).

PFS 2 was more mature compared to MONALEESA 7, with an event rate of 24% and 34% for the ribociclib and placebo arms, and an HR of 0.67 (0.5 – 0.89), indicating that the delay of disease progression is maintained beyond progression.

Similar to MONALEESA 7, OS findings were immature with an event rate of 15 and 21%, but estimates leaned towards supportive for the ribociclib arm, HR 0.670 (0.465 – 0.964). Considering the analysis plan, the MAH informed that 263 deaths for the next OS interim analysis are expected to be reached in approximately 1Q2020, and 351 deaths for the final analysis are expected to be reached in approximately 3Q2022. The CHMP recommends submitting remaining OS analyses when available.

The ORR supported the PFS result where ORR per investigator assessment was higher in the Kisqali arm (32.4%; 95% CI: 28.3, 36.6) compared to the placebo arm (21.5%; 95% CI:16.3, 26.7). In the audit sample, the ORR was 27.5% (21.2 – 33.8) for ribociclib vs. 15.5% (8.3 – 22.7) for placebo.

To evaluate patient-reported outcomes (PROs) for health-related quality of life (QoL) in the two treatment arms was described as a secondary objective in the two clinical studies, with no further specification. The protocols describe the analyses as well as others to be performed, but state that no formal statistical tests will be performed on PRO data and hence that no multiplicity adjustment will be applied. Based on this, the PRO data has not been considered important in determining the benefit/risk for the product in the claimed indication.

With regards to biomarkers analysis, CDK pathway relevant genes and their correlations with PFS were included in the initial submission. Additional exploratory biomarker analyses are ongoing in the two pivotal studies MONALEESA-7 and MONALEESA-3. Results are expected for both in Q2 2019. Preclinical findings (notably regarding non-functional retinoblastoma) indicate that there may be a molecularly well-defined group of patients with compromised benefit. The results of the exploratory biomarker analyses in MONALEESA 7 and 3 may provide relevant information in this regard and are expected to be submitted post authorisation as soon as available.

Of all patients who received Kisqali in studies MONALEESA-2 and MONALEESA-3, representative proportions of patients were ≥65 years and ≥75 years of age (see SmPC section 5.1). No overall differences in safety or effectiveness of Kisqali were observed between these patients and younger patients (see SmPC section 4.2).

The proposed indication included the following extrapolations from the two pivotal studies:

- From pre/perimenopausal women (Study E2301), and postmenopausal women (Study A2301, Study F2301) with HR-positive HER2-negative locally advanced or metastatic breast cancer to men with HR-positive HER2-negative locally advanced or metastatic breast cancer.

  Extrapolation to men patients has not been sufficiently justified and has been withdrawn by the MAH.

- From NSAI + LHRH as initial endocrine therapy in pre/perimenopausal patients (Study E2301), and from fulvestrant in postmenopausal patients who have received no or only one line of prior endocrine treatment (Study F2301), to combination with fulvestrant + LHRH in pre/perimenopausal women.

  The extrapolation to ribociclib in combination with fulvestrant + LHRH in pre/perimenopausal women can be accepted. The efficacy of ribociclib has been shown in combination with fulvestrant in post-menopausal women and in combination with AI in pre/perimenopausal women, which support extrapolation. Effective inhibition of ER signalling is achieved with AI or fulvestrant (+LHRH) alike, as this is the basis for anti-tumour activity of these compounds. This further supports that ribociclib can be used as add-on to AI +LHRH and also to fulvestrant +LHRH in pre/perimenopausal women.

- NSAI + LHRH as initial endocrine therapy in pre/perimenopausal patients (Study E2301), and from fulvestrant in postmenopausal patients who have received no or only one line of prior endocrine treatment (Study F2301) to combination with AI in patients who have received prior endocrine therapy

  The indication for second-line use of ribociclib in combination with AI can be supported by extrapolation from the demonstrated add-on effect to fulvestrant in the second line, in combination with evidence of efficacy in the first line in combination with AI.

- From NSAI (letrozole or anastrozole) (Study E2301) to any aromatase inhibitor (AI)

  Extrapolation from NSAI to any aromatase inhibitor is considered acceptable based on the similarity of the mechanism of action of aromatase inhibitors in general, where inhibition of the aromatase enzyme will block the conversion of androgens to oestrogens. There are no DDI/PK issues between exemestane or anastrozole and ribociclib that preclude the extrapolation (see EPAR Kisqali).

- From goserelin to any LHRH agonist (Study E2301)

Based on similarity of the mechanism of action of LHRH agonist in general, this extrapolation is considered acceptable.

2.4.4. Conclusions on the clinical efficacy

The PFS benefit of ribociclib observed in advanced disease in 1st line use as add on to a non-steroidal AI, and 2nd line use as add-on to fulvestrant is of clear clinical benefit. The MAH is recommended to submit remaining and final OS analyses as post-authorisation measures.

The available efficacy data is considered sufficient to support an indication in women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (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.

2.5. Clinical safety

Introduction

The approval of ribociclib was primarily based on the pivotal Phase III A2301 study (MONALEESA 2) in which ribociclib in combination with an AI was investigated in a population of HR positive, HER 2 negative postmenopausal women. The most common ADRs (frequency of reports ≥20 %) for which the frequency for the experimental arm exceeded that of the control arm included neutropenia, nausea, fatigue, diarrhea and vomiting. The most common grade 3/4 ADRs (frequency of reports ≥2 %) included neutropenia, leukopenia, abnormal liver function test, lymphopenia, hypophosphataemia, vomiting, nausea and fatigue.

The MAH submitted safety data from the two pivotal studies supporting this application, study F2301 (MONALEESA 3) and study E2301 (MONALEESA 7).

Study F2301 (LEE011F2301, MONALEESA 3)

The F2301 study is a randomized, double blind, placebo controlled Phase III study conducted in postmenopausal women with HR positive, HER2 negative advanced breast cancer as 1st or 2nd line (after only one line of prior endocrine treatment) in combination with fulvestrant vs. fulvestrant alone. Also men were eligible but none was enrolled.

The safety data base comprises data from the 483 patients exposed to ribociclib + fulvestrant in this study. There are also data submitted from an additional 13 patients exposed to the same regimen in the Phase Ib/II (dose-finding) X2108 study. The main focus for this assessment is on the Phase III study.

Patient exposure

Table 66: Duration of exposure to study treatment and study drug in Study F2301 (Safety set)

	Study F2301					
			Study drug			
	Study treatment		Ribociclib or matching placebo		Fulvestrant	
	RIBO + FULV N=483	PBO + FULV N=241	RIBO + FULV N=483	PBO + FULV N=241	RIBO + FULV N=483	PBO + FULV N=241
Duration of exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Exposure (mo)						
Mean (SD)	13.33 (7.903)	11.88 (7.753)	12.11 (8.300)	11.46 (7.919)	13.15 (7.765)	11.76 (7.629)
Median	15.77	11.96	12.65	11.07	15.77	11.96
Minimum – maximum	0.9 – 27.4	0.9 – 25.9	0 – 27.4	0.5 – 25.9	0.9 – 26.7	0.9 – 25.8
Exposure cagtegory – n (%)						
< 3 mo	92 (19.0)	54 (22.4)	118 (24.4)	56 (23.2)	93 (19.3)	54 (22.4)
3 to < 6 mo	45 (9.3)	27 (11.2)	50 (10.4)	32 (13.3)	44 (9.1)	27 (11.2)
6 to < 9 mo	30 (6.2)	16 (6.6)	36 (7.5)	16 (6.6)	30 (6.2)	16 (6.6)
9 to < 12 mo	37 (7.7)	25 (10.4)	31 (6.4)	23 (9.5)	37 (7.7)	25 (10.4)
12 to < 15 mo	31 (6.4)	19 (7.9)	21 (4.3)	17 (7.1)	31 (6.4)	19 (7.9)
15 to < 18 mo	59 (12.2)	26 (10.8)	54 (11.2)	24 (10.0)	77 (15.9)	34 (14.1)
≥ 18 mo	189 (39.1)	74 (30.7)	173 (35.8)	73 (30.3)	171 (35.4)	66 (27.4)
Patient-years	**536.4**	**238.7**	487.5	230.1	NA	NA

FULV = fulvestrant; NA = not available; PBO = placebo; RIBO = ribociclib; SD = standard deviation
Study treatment is defined as ribociclib in combination with fulvestrant or matching placebo in combination with fulvestrant. Study drug is defined as ribociclib, fulvestrant, or placebo.
Patient-years is calculated as the sum of exposure in years (y) across all patients.
Source: [SCS Study F2301-Appendix 1-Table 3-2.1], [SCS Study F2301-Appendix 1-Table 3-2.2], [Study F2301-Table 14.3-1.1]

Table 67: Number of patients with reduction, interruption, or dosing delays to study treatment in Study F2301 (Safety set)

	Study F2301			
	Ribociclib or matching placebo		Fulvestrant	
Exposure interruption, reduction, delay	RIBO + FULV N=483 n (%)	PBO + FULV N=241 n (%)	RIBO + FULV N=483 n (%)	PBO + FULV N=241 n (%)
Total no. of patients – n (%)	**483 (100)**	**241 (100)**	**483 (100)**	**241 (100)**
Number of reductions				
0	300 (62.1)	231 (95.9)	NA	NA
1	148 (30.6)	9 (3.7)	NA	NA
2	34 (7.0)	1 (0.4)	NA	NA
≥ 3	1 (0.2)	0	NA	NA
In at least one reduction, by reason				
Adverse event	160 (33.1)	8 (3.3)	NA	NA
Physician decision	16 (3.3)	0	NA	NA
Dosing error	10 (2.1)	2 (0.8)	NA	NA
Missing	2 (0.4)	0	NA	NA
Patient/guardian decision	1 (0.2)	0	NA	NA
Technical problems	1 (0.2)	0	NA	NA
Number of interruptions				
0	119 (24.6)	136 (56.4)	457 (94.6)	232 (96.3)
1	86 (17.8)	53 (22.0)	22 (4.6)	6 (2.5)
2	61 (12.6)	18 (7.5)	3 (0.6)	2 (0.8)
≥ 3	217 (44.9)	34 (14.1)	1 (0.2)	1 (0.4)
In at least one interruption, by reason				
Adverse event	331 (68.5)	45 (18.7)	20 (4.1)	7 (2.9)
Dosing error	111 (23.0)	43 (17.8)	1 (0.2)	0
Patient/guardian decision	67 (13.9)	27 (11.2)	0	1 (0.4)
Physician decision	56 (11.6)	20 (8.3)	4 (0.8)	2 (0.8)
Technical problems	25 (5.2)	9 (3.7)	1 (0.2)	0
Dispensing error	15 (3.1)	7 (2.9)	1 (0.2)	0
Number of delays				
0	235 (48.7)	174 (72.2)	NA	NA
1	77 (15.9)	45 (18.7)	NA	NA
2	53 (11.0)	9 (3.7)	NA	NA
≥ 3	118 (24.4)	13 (5.4)	NA	NA
In at least one delay, by reason				
Adverse event	217 (44.9)	25 (10.4)	NA	NA
Dosing error	35 (7.2)	24 (10.0)	NA	NA
Physician decision	30 (6.2)	13 (5.4)	NA	NA
Patient/guardian decision	26 (5.4)	15 (6.2)	NA	NA
Technical problems	19 (3.9)	9 (3.7)	NA	NA
Dispensing error	5 (1.0)	5 (2.1)	NA	NA

An interruption is defined as 0-mg dose entered on the CRF ≥ 1 d when the dose interruption box checked. A dosing break with ribociclib/placebo on Days 22 to 28 of any cycle is not counted as an interruption. Delay is the subset of an interruption that occurs at the beginning of a new cycle after a rest period, and dosing delay is only applicable to ribociclib/placebo.
Source: [Study F2301-Table 14.3-1.3]

Table 68: Patient disposition in Study F2301 (Safety set)

	Study F2301	
	RIBO + FULV	PBO + FULV
	N=483	N=241
Disposition reason	**n (%)**	**n (%)**
Treated[1]	**483 (100)**	**241 (100)**
Ongoing	204 (42.2)	76 (31.5)
End of treatment	279 (57.8)	165 (68.5)
Primary reason for end of treatment		
Progressive disease	193 (40.0)	142 (58.9)
Adverse event	41 (8.5)	10 (4.1)
Physician decision	22 (4.6)	7 (2.9)
Patient/guardian[2] decision	20 (4.1)	5 (2.1)
Protocol deviation	1 (0.2)	1 (0.4)
Death	2 (0.4)	0
Entered posttreatment efficacy follow-up[3]	**25 (9.0)**	**7 (4.2)**
No longer followed in posttreatment efficacy follow-up	15 (5.4)	5 (3.0)
Followed in posttreatment efficacy follow-up	10 (3.6)	2 (1.2)
Primary reason for end of posttreatment efficacy follow-up[4]	**15 (60.0)**	**5 (71.4)**
Progressive disease	9 (36.0)	3 (42.9)
Patient/guardian[2] decision	4 (16.0)	1 (14.3)
Death	2 (8.0)	1 (14.3)

As of Study F2301 DCO, 03-Nov-2017 (Table 1-1)
[1] All percentages use the number of patients treated as the denominator.
[2] Patient/guardian decides to no longer continue to participate, which was carefully followed for exclusion of other possibilities of underlying cause (e.g. lack of efficacy).
[3] The percentage of patients who entered posttreatment follow-up uses the number patient with end-of-treatment as the denominator.
[4] Patients who enter and then discontinue from the posttreatment follow-up phase: the number of patients who entered posttreatment follow-up is used as the denominator.
Source: [SCS Study F2301-Appendix 1-Table 3-1.1].

Adverse events

Table 69: Adverse event categories in Study F2301 (Safety set)

	Study F2301					
	RIBO + FULV N=483			PBO + FULV N=241		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All deaths[1]	70 (14.5)	NA	NA	50 (20.7)	NA	NA
On-treatment deaths[2]	13 (2.7)	NA	NA	8 (3.3)	NA	NA
AEs	479 (99.2)	309 (64.0)	69 (14.3)	231 (95.9)	61 (25.3)	10 (4.1)
Suspected to be drug related	461 (95.4)	274 (56.7)	52 (10.8)	164 (68.0)	16 (6.6)	3 (1.2)
SAEs	138 (28.6)	91 (18.8)	23 (4.8)	40 (16.6)	27 (11.2)	7 (2.9)
Suspected to be drug related	54 (11.2)	33 (6.8)	11 (2.3)	6 (2.5)	3 (1.2)	1 (0.4)
AEs leading to discontinuation	83 (17.2)	36 (7.5)	12 (2.5)	15 (6.2)	9 (3.7)	1 (0.4)
Suspected to be drug related	68 (14.1)	29 (6.0)	8 (1.7)	8 (3.3)	4 (1.7)	0
AEs requiring dose interruption and/or adjustment	361 (74.7)	266 (55.1)	39 (8.1)	55 (22.8)	18 (7.5)	5 (2.1)
Suspected to be drug related	330 (68.3)	250 (51.8)	34 (7.0)	25 (10.4)	8 (3.3)	1 (0.4)
AEs requiring additional therapy	420 (87.0)	157 (32.5)	17 (3.5)	189 (78.4)	44 (18.3)	4 (1.7)
Suspected to be drug related	295 (61.1)	84 (17.4)	9 (1.9)	67 (27.8)	4 (1.7)	0
AESIs	444 (91.9)	270 (55.9)	56 (11.6)	156 (64.7)	28 (11.6)	4 (1.7)
Suspected to be drug related	396 (82.0)	252 (52.2)	47 (9.7)	43 (17.8)	7 (2.9)	2 (0.8)

[1] Patients with AE outcome of fatal include all deaths > 30 d after last date of study treatment.
[2] Death that occurs > 30 d after last date of study treatment not included.
Source: [Study F2301-Table 14.3.1-1.1]

Table 70: Adverse events by system organ class in Study F2301 (Safety set)

Primary system organ class	Study F2301					
	RIBO + FULV N=483			PBO + FULV N=241		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	**479 (99.2)**	**309 (64.0)**	**69 (14.3)**	**231 (95.9)**	**61 (25.3)**	**10 (4.1)**
Gastrointestinal disorders	374 (77.4)	30 (6.2)	0	141 (58.5)	7 (2.9)	0
General disorders and administration site conditions	303 (62.7)	15 (3.1)	2 (0.4)	152 (63.1)	4 (1.7)	0
Blood and lymphatic system disorders	295 (61.1)	191 (39.5)	30 (6.2)	17 (7.1)	5 (2.1)	0
Skin and subcutaneous tissue disorders	273 (56.5)	12 (2.5)	0	62 (25.7)	0	0
Musculoskeletal and connective tissue disorders	267 (55.3)	22 (4.6)	0	161 (66.8)	7 (2.9)	0
Infections and infestations	257 (53.2)	29 (6.0)	0	95 (39.4)	6 (2.5)	0
Investigations	256 (53.0)	125 (25.9)	24 (5.0)	63 (26.1)	12 (5.0)	3 (1.2)
Nervous system disorders	217 (44.9)	17 (3.5)	4 (0.8)	92 (38.2)	5 (2.1)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	201 (41.6)	19 (3.9)	4 (0.8)	87 (36.1)	13 (5.4)	2 (0.8)
Metabolism and nutrition disorders	161 (33.3)	31 (6.4)	3 (0.6)	62 (25.7)	10 (4.1)	1 (0.4)
Vascular disorders	154 (31.9)	23 (4.8)	4 (0.8)	76 (31.5)	12 (5.0)	0
Psychiatric disorders	120 (24.8)	6 (1.2)	0	56 (23.2)	3 (1.2)	0
Eye disorders	101 (20.9)	3 (0.6)	0	23 (9.5)	0	0
Injury, poisoning and procedural complications	80 (16.6)	11 (2.3)	1 (0.2)	38 (15.8)	4 (1.7)	2 (0.8)
Renal and urinary disorders	62 (12.8)	9 (1.9)	0	17 (7.1)	0	0
Cardiac disorders	44 (9.1)	11 (2.3)	3 (0.6)	21 (8.7)	2 (0.8)	0
Ear and labyrinth disorders	41 (8.5)	1 (0.2)	0	7 (2.9)	0	0
Reproductive system and breast disorders	35 (7.2)	1 (0.2)	0	25 (10.4)	0	0
Neoplasms benign, malignant unspec (incl cysts polyps)	21 (4.3)	3 (0.6)	1 (0.2)	11 (4.6)	5 (2.1)	1 (0.4)
Immune system disorders	18 (3.7)	1 (0.2)	0	3 (1.2)	0	0
Hepatobiliary disorders	17 (3.5)	5 (1.0)	3 (0.6)	8 (3.3)	3 (1.2)	0
Endocrine disorders	7 (1.4)	0	0	2 (0.8)	0	1 (0.4)
Surgical and medical procedures	4 (0.8)	2 (0.4)	0	1 (0.4)	0	0

Primary SOCs are sorted in descending frequency as reported in the ribociclib treatment column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple events is counted only once in the total row.
MedDRA Version 20.1 was used.
Source: [Study F2301-Table 14.3.1-1.2]

Table 71: AEs by PT (≥ 10% in any group) irrespective of causality in Study F2301 (Safety set)

	Study F2301					
	RIBO + FULV N=483			PBO + FULV N=241		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	**479 (99.2)**	**309 (64.0)**	**69 (14.3)**	**231 (95.9)**	**61 (25.3)**	**10 (4.1)**
Neutropenia	270 (55.9)	177 (36.6)	28 (5.8)	2 (0.8)	0	0
Nausea	219 (45.3)	7 (1.4)	0	68 (28.2)	2 (0.8)	0
Fatigue	152 (31.5)	8 (1.7)	0	80 (33.2)	1 (0.4)	0
Diarrhoea	140 (29.0)	3 (0.6)	0	49 (20.3)	2 (0.8)	0
Vomiting	129 (26.7)	7 (1.4)	0	31 (12.9)	0	0
Constipation	120 (24.8)	4 (0.8)	0	28 (11.6)	0	0
Arthralgia	116 (24.0)	3 (0.6)	0	64 (26.6)	1 (0.4)	0
Cough	105 (21.7)	0	0	37 (15.4)	0	0
Headache	104 (21.5)	4 (0.8)	0	49 (20.3)	1 (0.4)	0
Pruritus	96 (19.9)	1 (0.2)	0	16 (6.6)	0	0
Alopecia	90 (18.6)	0	0	11 (4.6)	0	0
Neutrophil count decreased	89 (18.4)	64 (13.3)	5 (1.0)	3 (1.2)	0	0
Rash	89 (18.4)	2 (0.4)	0	14 (5.8)	0	0
Back pain	85 (17.6)	8 (1.7)	0	42 (17.4)	2 (0.8)	0
Anaemia	80 (16.6)	15 (3.1)	0	13 (5.4)	5 (2.1)	0
Decreased appetite	78 (16.1)	1 (0.2)	0	31 (12.9)	0	0
Leukopenia	77 (15.9)	25 (5.2)	2 (0.4)	0	0	0
Dyspnoea	72 (14.9)	6 (1.2)	1 (0.2)	30 (12.4)	4 (1.7)	0
Alanine aminotransferase increased	70 (14.5)	32 (6.6)	9 (1.9)	11 (4.6)	1 (0.4)	0
Asthenia	69 (14.3)	2 (0.4)	0	31 (12.9)	1 (0.4)	0
Pain in extremity	66 (13.7)	3 (0.6)	0	39 (16.2)	2 (0.8)	0
Aspartate aminotransferase increased	64 (13.3)	23 (4.8)	6 (1.2)	11 (4.6)	2 (0.8)	0
Hot flush	64 (13.3)	0	0	41 (17.0)	0	0
Dizziness	63 (13.0)	1 (0.2)	0	19 (7.9)	0	0
Oedema peripheral	60 (12.4)	0	0	12 (5.0)	0	0
White blood cell count decreased	59 (12.2)	34 (7.0)	0	2 (0.8)	0	0
Insomnia	58 (12.0)	1 (0.2)	0	26 (10.8)	0	0
Pyrexia	54 (11.2)	1 (0.2)	0	17 (7.1)	0	0
Abdominal pain upper	52 (10.8)	1 (0.2)	0	16 (6.6)	0	0
Nasopharyngitis	52 (10.8)	0	0	25 (10.4)	0	0
Urinary tract infection	50 (10.4)	5 (1.0)	0	24 (10.0)	3 (1.2)	0
Hypertension	48 (9.9)	20 (4.1)	1 (0.2)	24 (10.0)	11 (4.6)	0
Musculoskeletal pain	39 (8.1)	1 (0.2)	0	32 (13.3)	0	0

Preferred terms (PTs) are sorted in descending frequency of all grades column, as reported in the ribociclib treatment column.
A patient with multiple occurrences of an AE under one treatment is counted only once under the maximum grade in the AE category for that treatment.
A patient with multiple events is counted only once in the total row.
MedDRA Version 20.1 was used.
Source: [Study F2301-Table 14.3.1-1.4]

Serious adverse event / deaths / other significant events

Serious adverse event

Table 72: SAEs by PT irrespective of causality (at least 1% in any group) in Study F2301 (Safety set)

	Study F2301					
	RIBO + FULV N=483			PBO + FULV N=241		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	**138 (28.6)**	**91 (18.8)**	**23 (4.8)**	**40 (16.6)**	**27 (11.2)**	**7 (2.9)**
Pneumonia	9 (1.9)	8 (1.7)	0	0	0	0
Nausea	7 (1.4)	5 (1.0)	0	0	0	0
Vomiting	7 (1.4)	5 (1.0)	0	1 (0.4)	0	0
Anaemia	6 (1.2)	3 (0.6)	0	0	0	0
Dyspnoea	6 (1.2)	5 (1.0)	0	5 (2.1)	4 (1.7)	0
Neutropenia	6 (1.2)	3 (0.6)	1 (0.2)	0	0	0
Pleural effusion	6 (1.2)	4 (0.8)	1 (0.2)	3 (1.2)	2 (0.8)	0
Abdominal pain	5 (1.0)	5 (1.0)	0	1 (0.4)	1 (0.4)	0
Acute kidney injury	5 (1.0)	4 (0.8)	0	0	0	0
Febrile neutropenia	5 (1.0)	5 (1.0)	0	0	0	0
Pyrexia	5 (1.0)	1 (0.2)	0	1 (0.4)	0	0

PTs are sorted in descending frequency of all grades column, as reported in the ribociclib treatment column.
A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment.
A patient with multiple events is counted only once in the total row.
MedDRA Version 20.1 was used.
Source: [Study F2301-Table 14.3.1-1.9]

Deaths

Table 73: On-treatment deaths by PT irrespective of causality in Study F2301 (Safety set)

	Study F2301	
Primary cause of death Preferred term	RIBO + FULV N=483 n (%)	PBO + FULV N=241 n (%)
Total	**13 (2.7)**	**8 (3.3)**
Study indication	7 (1.4)	7 (2.9)
Other	6 (1.2)	1 (0.4)
Pulmonary embolism	1 (0.2)	1 (0.4)
Acute respiratory distress syndrome	1 (0.2)	0
Cardiac failure	1 (0.2)	0
Pneumonia	1 (0.2)	0
Shock haemorrhagic	1 (0.2)	0
Ventricular arrhythmia	1 (0.2)	0

PTs are sorted by descending frequency, as reported in the ribociclib treatment column.
Deaths occurring up to 30 d, inclusive, after last dose of study treatment are included.
MedDRA Version 20.1 was used.
Source: [Study F2301-Table 14.3.1-1.6], [Study F2301-Listing 14.3.2-1.1]

AEs of Special Interest (AESIs)

<u>QT interval prolongation and QTc</u>

QT interval prolongation was observed at a higher proportion with the ribociclib and fulvestrant combination (7.7%) as compared to the control arm (2.1%). The most frequent event within this AESI was prolonged electrocardiogram QT. No case of Torsades de Pointes or sudden death occurred.

Based on central assessment of electrocardiogram (ECGs), 27 patients (5.6 %) in the test arm experienced a new QTc using Fridericia's formula (QTcF) intervals > 480 ms post-baseline including 8 patients (1.7 %) with a QTcF > 500 ms. A > 60 ms increase from baseline in QTcF interval was observed in 31 patients (6.5 %).

Hepatobiliary toxicity events

An increased hepatobiliary toxicity was observed in ribociclib + fulvestrant exposed patients (21.7%) in the F2301 study as compared to the control arm (14.9%). The two most frequent events within this AESI were increased ALT and increased AST at approximately similar rates.

Based on clinical and laboratory data review, seven patients met the biochemical criteria for Hy's Law and of these, two patients were confirmed Hy's Law. Both patients permanently discontinued ribociclib and their liver function tests returned to baseline values. Both patients received ribociclib in combination with fulvestrant.

Laboratory findings

In the F2301 study the most frequently reported post-baseline haematological abnormalities (all grades) in the experimental arm (with a ≥10% difference relative to the control arm) were decreased neutrophils (+71.0 %), decreased leukocytes (+68.7 %), decreased lymphocytes (+34.0 %), and decreased hemoglobin (+25.3 %). The majority of grade 3 abnormalities reported were decreased neutrophil and leukocyte counts whilst grade 4 was predominantly decreased neutrophil counts.

In terms of post-baseline clinical chemistry abnormalities the most frequently reported (all grades) in the experimental arm (with a ≥ 5% difference relative to the control arm) were increased creatinine (+32.4 %), decreased phosphate (+9.3 %), increased ALT (+6.6 %), and increased AST (+6.3 %). Elevations in ALT and GGT were frequent grade 3 abnormalities whilst grade 4 was primarily due to elevated ALT.

Safety in special populations

All patients in the F2301 study were female. In terms of race, the vast majority was Caucasian (84 % and 88 % in the test and control arm respectively). Asian patients enrolled were few (9 % and 8 % in the respective arms) thus hampering any conclusion on safety by race. In regard to safety by age categories (< 65 y vs. ≥ 65 y) haematological AESIs was comparable between the two categories with the exception of neutropenia (72.4% vs. 66.4% respectively). The following were reported in a higher proportion in the younger age cohort as compared to the ≥ 65 years: infections (57.6 % vs. 48.7 %), hepatobiliary toxicities (24.1 % vs. 19.0 %), infection-related AEs (11.3 % vs. 8.8 % including SAEs [7.0 % vs. 4.9 %]), hepatobiliary toxicity related AEs (grade 3/4 AEs [15.2 % vs. 10.2 %], suspected AEs [20.2 % vs. 16.4 %] and AEs needing dose adjustments or interruptions [16.7 % vs. 9.3 %]).

The following AESIs were higher in proportion in patients ≥65 years: pulmonary toxicities, respiratory disorders (38.5 % vs. 28.8 % including grade 3/4 AEs [3.5 % vs. 0.4 %], SAEs [2.7 % vs. 0.8 %]) and renal toxicities (14.2 % vs. 7.0 %).

Discontinuation due to adverse events

Table 74: AEs leading to discontinuation by PT irrespective of causality (at least 1% in any group) in Study F2301 (Safety set)

	Study F2301					
	RIBO + FULV N=483			PBO + FULV N=241		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	83 (17.2)	36 (7.5)	12 (2.5)	15 (6.2)	9 (3.7)	1 (0.4)
Alanine aminotransferase increased	22 (4.6)	6 (1.2)	5 (1.0)	0	0	0
Aspartate aminotransferase increased	13 (2.7)	3 (0.6)	3 (0.6)	1 (0.4)	1 (0.4)	0
Vomiting	5 (1.0)	1 (0.2)	0	0	0	0

PTs are sorted in descending frequency of all grades column, as reported in the ribociclib treatment column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs is counted only once in the total row.
AEs leading to discontinuation refers to any component of study treatment.
MedDRA Version 20.1 was used.
Source: [Study F2301-Table 14.3.1-1.11]

Study E2301 (CLEE011E2301, MONALEESA 7)

The E2301 study is a randomised (1:1), double blind, placebo-controlled Phase III study conducted in pre and perimenopausal women with HR positive, HER2 negative advanced breast cancer in combination with a NSAI or tamoxifen plus goserelin vs. placebo in combination with a NSAI or tamoxifen plus goserelin. The safety data base comprises data from the 248 patients exposed to ribociclib + NSAI in this study. There are also data submitted from an additional 47 patients exposed to the same regimen in the Phase Ib, dose-escalation/expansion X2107 study.

The main focus for this assessment is on the Phase III study and on the combination of ribociclib with NSAI. Data cut- off date: 20 Aug 2017.

In some tables, reference is made to study A2301 (MONALEESA 2) which is the Phase III clinical study conducted in HR positive, HER 2 negative postmenopausal women with advanced breast cancer with ribociclib in combination with an AI as 1st line therapy (see EPAR Kisqali and SmPC Section 5.1).

Patient exposure

Table 75: Duration of exposure to study treatment in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO + LET/ANA[1]	PBO + LET/ANA[1]	RIBO + LET	PBO + LET	RIBO + LET	RIBO + NSAI[1]	PBO + NSAI[1]
Duration of exposure (months)	N = 248	N = 247	N = 334	N = 330	N = 47	N = 629	N = 577
Exposure categories (months) – n (%)							
< 3	28 (11.3)	53 (21.5)	40 (12.0)	47 (14.2)	11 (23.4)	79 (12.6)	100 (17.3)
3 - < 6	15 (6.0)	24 (9.7)	33 (9.9)	28 (8.5)	8 (17.0)	56 (8.9)	52 (9.0)
6 - < 9	17 (6.9)	22 (8.9)	21 (6.3)	31 (9.4)	6 (12.8)	44 (7.0)	53 (9.2)
9 - < 12	21 (8.5)	22 (8.9)	29 (8.7)	34 (10.3)	3 (6.4)	53 (8.4)	56 (9.7)
12 - < 15	39 (15.7)	33 (13.4)	17 (5.1)	34 (10.3)	4 (8.5)	60 (9.5)	67 (11.6)
15 - < 18	49 (19.8)	35 (14.2)	18 (5.4)	24 (7.3)	1 (2.1)	68 (10.8)	59 (10.2)
≥ 18	79 (31.9)	58 (23.5)	176 (52.7)	132 (40.0)	14 (29.8)	269 (42.8)	190 (32.9)
Exposure (months)							
Mean (SD)	14.4 (7.13)	11.7 (7.59)	17.2 (9.98)	15.1 (9.41)	12.5 (10.66)	15.7 (9.15)	13.6 (8.83)
Median	15.3	12.8	20.2	14.1	8.3	16	13.2
Min, Max	0, 30	1, 30	0, 34	0, 32	2, 35	0, 35	0, 32
Patient-years	**297.7**	**241.1**	**478.6**	**414.7**	**49.0**	**825.4**	**655.7**

Min, Max=Minimum, Maximum; NSAI=non-steroidal aromatoase inhibitor; PBO=placebo; RIBO=ribociclib; LET=letrozole; ANA=anastrazole.
[1]For Study E2301, only patients assigned to NSAI (letrozole or anastrozole) in treatment assignment CRF are included.
Study treatment includes any medication that is part of study treatment.
Patient-years is calculated as the sum of exposure (in years) across all patients.
Source: [SCS Study E2301-Appendix 1-Table 3-2.1]

Table 76: Dose reductions, interruptions, and delays of ribociclib/placebo in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO + LET/ANA[1]	PBO + LET/ANA[1]	RIBO + LET	PBO + LET	RIBO + LET	RIBO + NSAI[1]	PBO + NSAI[1]
Exposure variable	**N = 248**	**N = 247**	**N = 334**	**N = 330**	**N = 47**	**N = 629**	**N = 577**
Total number of patients received ribociclib/placebo	**246**	**245**	**334**	**330**	**47**	**627**	**575**
Reductions							
Number of reductions							
0	155 (63.0)	227 (92.7)	142 (42.5)	304 (92.1)	36 (76.6)	333 (53.1)	531 (92.3)
1	66 (26.8)	14 (5.7)	115 (34.4)	20 (6.1)	10 (21.3)	191 (30.5)	34 (5.9)
2	23 (9.3)	4 (1.6)	70 (21.0)	5 (1.5)	1 (2.1)	94 (15.0)	9 (1.6)
≥ 3	2 (0.8)	0	7 (2.1)	1 (0.3)	0	9 (1.4)	1 (0.2)
Number of patients with at least one dose reduction by reason							
Adverse event	82 (33.3)	15 (6.1)	182 (54.5)	14 (4.2)	5 (10.6)	269 (42.9)	29 (5.0)
Dosing error	6 (2.4)	3 (1.2)	8 (2.4)	7 (2.1)	3 (6.4)	17 (2.7)	10 (1.7)
Physician decision	4 (1.6)	1 (0.4)	7 (2.1)	2 (0.6)	0	11 (1.8)	3 (0.5)
Subject/guardian decision	1 (0.4)	0	8 (2.4)	2 (0.6)	0	9 (1.4)	2 (0.3)
Missing	1 (0.4)	0	0	0	3 (6.4)	4 (0.6)	0
As per protocol	0	0	0	0	1 (2.1)	1 (0.2)	0
Lack of efficacy	0	0	1 (0.3)	1 (0.3)	0	1 (0.2)	1 (0.2)
Interruptions							
Number of interruptions							
0	54 (22.0)	151 (61.6)	68 (20.4)	184 (55.8)	9 (19.1)	131 (20.9)	335 (58.3)
1	44 (17.9)	44 (18.0)	56 (16.8)	61 (18.5)	12 (25.5)	112 (17.9)	105 (18.3)
2	39 (15.9)	26 (10.6)	44 (13.2)	38 (11.5)	11 (23.4)	94 (15.0)	64 (11.1)
≥ 3	109 (44.3)	24 (9.8)	166 (49.7)	47 (14.2)	15 (31.9)	290 (46.3)	71 (12.3)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO + LET/ANA[1]	PBO + LET/ANA[1]	RIBO + LET	PBO + LET	RIBO + LET	RIBO + NSAI[1]	PBO + NSAI[1]
Exposure variable	**N = 248**	**N = 247**	**N = 334**	**N = 330**	**N = 47**	**N = 629**	**N = 577**
Number of patients with at least one dose interruption by reason							
Adverse event	172 (69.9)	38 (15.5)	239 (71.6)	54 (16.4)	25 (53.2)	436 (69.5)	92 (16.0)
Dosing error	58 (23.6)	48 (19.6)	87 (26.0)	80 (24.2)	10 (21.3)	155 (24.7)	128 (22.3)
Subject/guardian decision	22 (8.9)	12 (4.9)	40 (12.0)	32 (9.7)	12 (25.5)	74 (11.8)	44 (7.7)
Physician decision	14 (5.7)	13 (5.3)	33 (9.9)	16 (4.8)	8 (17.0)	55 (8.8)	29 (5.0)
Technical problems	8 (3.3)	5 (2.0)	20 (6.0)	13 (3.9)	4 (8.5)	32 (5.1)	18 (3.1)
Dispensing error	5 (2.0)	5 (2.0)	8 (2.4)	11 (3.3)	0	13 (2.1)	16 (2.8)
Disease progression	0	0	0	0	1 (2.1)	1 (0.2)	0
Protocol deviation	0	0	0	0	1 (2.1)	1 (0.2)	0
Delays							
Number of delays							
0	101 (41.1)	202 (82.4)	133 (39.8)	241 (73.0)	33 (70.2)	267 (42.6)	443 (77.0)
1	47 (19.1)	29 (11.8)	72 (21.6)	47 (14.2)	10 (21.3)	129 (20.6)	76 (13.2)
2	22 (8.9)	10 (4.1)	37 (11.1)	22 (6.7)	4 (8.5)	63 (10.0)	32 (5.6)
≥ 3	76 (30.9)	4 (1.6)	92 (27.5)	20 (6.1)	0	168 (26.8)	24 (4.2)
Number of patients with at least one delay by reason							
Adverse event	132 (53.7)	14 (5.7)	170 (50.9)	31 (9.4)	12 (25.5)	314 (50.1)	45 (7.8)
Dosing error	15 (6.1)	13 (5.3)	46 (13.8)	40 (12.1)	1 (2.1)	62 (9.9)	53 (9.2)
Physician decision	9 (3.7)	6 (2.4)	23 (6.9)	13 (3.9)	2 (4.3)	34 (5.4)	19 (3.3)
Subject/guardian decision	9 (3.7)	6 (2.4)	23 (6.9)	17 (5.2)	1 (2.1)	33 (5.3)	23 (4.0)
Technical problems	4 (1.6)	4 (1.6)	13 (3.9)	13 (3.9)	0	17 (2.7)	17 (3.0)
Dispensing error	3 (1.2)	4 (1.6)	6 (1.8)	5 (1.5)	0	9 (1.4)	9 (1.6)

LET=letrozole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib; ANA=anastrazole
[1]For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Total number of patients received ribociclib/placebo is used as the denominator
For Study A2301 only, discontinuation of ribociclib/placebo while remaining on study treatment is considered as a dose reduction
Delays are the subset of interruptions that occur at the beginning of a new cycle after a rest period.
Source: [SCS Study E2301-Appendix 1-Table 3-2.4]

Table 77: Patient disposition in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO + LET/ANA[1]	PBO + LET/ANA[1]	RIBO + LET	PBO + LET	RIBO + LET	RIBO + NSAI[1]	PBO + NSAI[1]
	N = 248	N = 247	N = 334	N = 330	N = 47	N = 629	N = 577
Disposition reason	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated[2]	**248 (100.0)**	**247 (100.0)**	**334 (100)**	**330 (100)**	**47 (100)**	**629 (100.0)**	**577 (100.0)**
Treatment ongoing[3]	131 (52.8)	93 (37.7)	131 (39.2)	88 (26.7)	10 (21.3)	272 (43.2)	181 (31.4)
End of treatment	117 (47.2)	154 (62.3)	203 (60.8)	242 (73.3)	37 (78.7)	357 (56.8)	396 (68.6)
Reason for end of treatment[2]							
Progressive disease	88 (35.5)	125 (50.6)	133 (39.8)	203 (61.5)	29 (61.7)	250 (39.7)	328 (56.8)
Adverse event	8 (3.2)	6 (2.4)	27 (8.1)	8 (2.4)	2 (4.3)	37 (5.9)	14 (2.4)
Subject/guardian decision	13 (5.2)	7 (2.8)	20 (6.0)	16 (4.8)	1 (2.1)	34 (5.4)	23 (4.0)
Physician decision	6 (2.4)	12 (4.9)	16 (4.8)	13 (3.9)	5 (10.6)	27 (4.3)	25 (4.3)
Death	0	3 (1.2)	4 (1.2)	1 (0.3)	0	4 (0.6)	4 (0.7)
Protocol deviation	0	1 (0.4)	3 (0.9)	1 (0.3)	0	3 (0.5)	2 (0.3)
Lost to follow-up	2 (0.8)	0	0	0	0	2 (0.3)	0
Entered post-treatment efficacy follow-up[4]	**7 (6.0)**	**4 (2.6)**	**18 (8.9)**	**7 (2.9)**	**3 (8.1)**	**28 (7.8)**	**11 (2.8)**
No longer being followed in post-treatment follow-up	5 (4.3)	2 (1.3)	6 (3.0)	4 (1.7)	2 (5.4))	13 (3.6)	6 (1.5)
Continue to be followed in post-treatment follow-up	2 (1.7)	2 (1.3)	12 (5.9)	3 (1.2)	1 (2.7)	15 (4.2)	5 (1.3)
Reason for end of post-treatment follow-up[5]	**5 (71.4)**	**2 (50.0)**	**6 (33.3)**	**4 (57.1)**	**2 (66.7)**	**13 (46.4)**	**6 (54.5)**
Progressive disease	4 (57.1)	1 (25.0)	4 (22.2)	3 (42.9)	0	8 (28.6)	4 (36.4)
Subject/guardian decision	1 (14.3)	0	2 (11.1)	0	0	3 (10.7)	0
Death	0	1 (25.0)	0	1 (14.3)	0	0	2 (18.2)
New therapy for study indication	0	0	0	0	2 (66.7)	2 (7.1)	0

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
[2] All percentages in this section use the number treated as the denominator.
[3] Patients continue study treatment at the time of the cut-off.
[4] The percentage of patients who entered post-treatment follow-up uses the number discontinued from treatment as the denominator.
[5] Patients enter and discontinued from the post-treatment follow-up phase. In this section the denominator = the number of patients who entered post-treatment follow-up.
Source: [SCS Study E2301-Appendix 1-Table 3-1.1]

Adverse events

Table 78: Summary of deaths and adverse events in Study E2301 (Safety Set)

	Study E2301				Study A2301				Study X2107		Pooled data			
	RIBO+LET/ANA[1] N=248		PBO+LET/ANA[1] N=247		RIBO+LET N=334		PBO+LET N=330		RIBO+LET N=47		RIBO+NSAI[1] N=629		PBO+NSAI[1] N=577	
Adverse event category	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Adverse events	**242 (97.6)**	**191 (77.0)**	**229 (92.7)**	**77 (31.2)**	**331 (99.1)**	**288 (86.2)**	**322 (97.6)**	**123 (37.3)**	**47 (100)**	**41 (87.2)**	**620 (98.6)**	**520 (82.7)**	**551 (95.5)**	**200 (34.7)**
Suspected to be drug-related	230 (92.7)	172 (69.4)	173 (70.0)	25 (10.1)	323 (96.7)	254 (76.0)	258 (78.2)	31 (9.4)	46 (97.9)	34 (72.3)	599 (95.2)	460 (73.1)	431 (74.7)	56 (9.7)
All deaths[2]	**30 (12.1)**	**0**	**36 (14.6)**	**0**	**50 (15.0)**	**0**	**65 (19.7)**	**0**	**0**	**0**	**80 (12.7)**	**0**	**101 (17.5)**	**0**
On-treatment deaths[3]	1 (0.4)	0	5 (2.0)	0	7 (2.1)	0	3 (0.9)	0	0	0	8 (1.3)	0	8 (1.4)	0
Serious adverse events	**42 (16.9)**	**34 (13.7)**	**33 (13.4)**	**27 (10.9)**	**85 (25.4)**	**73 (21.9)**	**51 (15.5)**	**35 (10.6)**	**10 (21.3)**	**9 (19.1)**	**137 (21.8)**	**116 (18.4)**	**84 (14.6)**	**62 (10.7)**
Suspected to be drug-related	12 (4.8)	10 (4.0)	4 (1.6)	2 (0.8)	28 (8.4)	25 (7.5)	5 (1.5)	3 (0.9)	3 (6.4)	3 (6.4)	43 (6.8)	38 (6.0)	9 (1.6)	5 (0.9)
AEs leading to discontinuation	**16 (6.5)**	**12 (4.8)**	**8 (3.2)**	**6 (2.4)**	**56 (16.8)**	**39 (11.7)**	**13 (3.9)**	**8 (2.4)**	**2 (4.3)**	**2 (4.3)**	**74 (11.8)**	**53 (8.4)**	**21 (3.6)**	**14 (2.4)**
Suspected to be drug-related	13 (5.2)	8 (3.2)	3 (1.2)	2 (0.8)	48 (14.4)	32 (9.6)	6 (1.8)	1 (0.3)	2 (4.3)	2 (4.3)	63 (10.0)	42 (6.7)	9 (1.6)	3 (0.5)
AEs requiring dose interruption	**180 (72.6)**	**165 (66.5)**	**47 (19.0)**	**26 (10.5)**	**251 (75.1)**	**213 (63.8)**	**57 (17.3)**	**18 (5.5)**	**24 (51.1)**	**20 (42.6)**	**455 (72.3)**	**398 (63.3)**	**104 (18.0)**	**44 (7.6)**
Suspected to be drug-related	167 (67.3)	157 (63.3)	26 (10.5)	12 (4.9)	228 (68.3)	197 (59.0)	25 (7.6)	7 (2.1)	22 (46.8)	18 (38.3)	417 (66.3)	372 (59.1)	51 (8.8)	19 (3.3)
AEs requiring dose adjustment	**83 (33.5)**	**66 (26.6)**	**11 (4.5)**	**5 (2.0)**	**160 (47.9)**	**123 (36.8)**	**10 (3.0)**	**3 (0.9)**	**7 (14.9)**	**4 (8.5)**	**250 (39.7)**	**193 (30.7)**	**21 (3.6)**	**8 (1.4)**
Suspected to be drug-related	79 (31.9)	62 (25.0)	9 (3.6)	4 (1.6)	159 (47.6)	121 (36.2)	9 (2.7)	3 (0.9)	7 (14.9)	4 (8.5)	245 (39.0)	187 (29.7)	18 (3.1)	7 (1.2)
AEs requiring additional therapy	**211 (85.1)**	**81 (32.7)**	**186 (75.3)**	**44 (17.8)**	**306 (91.6)**	**139 (41.6)**	**284 (86.1)**	**78 (23.6)**	**40 (85.1)**	**13 (27.7)**	**557 (88.6)**	**233 (37.0)**	**470 (81.5)**	**122 (21.1)**

All=All grades; G 3/4=grade 3/4; LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
[2] All deaths including those >30 days after last date of study treatment.
[3] Deaths occurring >30 days after last date of study treatment are not included.
Suspected to be drug related refers to any component of study treatment.
Additional therapy includes all non-drug therapy and concomitant medications.
Discontinuation refers to discontinuation of any treatment component.
AEs up to 30 days after the last date of study treatment are included.
Source: [SCS Study E2301-Appendix 1-Table 3-4.1.1]

Table 79: Adverse events by primary system organ class, irrespective of causality in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
Primary system organ class	RIBO+LET/ANA[1] N=248	PBO+LET/ANA[1] N=247	RIBO+LET N=334	PBO+LET N=330	RIBO+LET N=47	RIBO+NSAI[1] N=629	PBO+NSAI[1] N=577
Any primary system organ class	**242 (97.6)**	**229 (92.7)**	**331 (99.1)**	**322 (97.6)**	**47 (100)**	**620 (98.6)**	**551 (95.5)**
Gastrointestinal disorders	165 (66.5)	140 (56.7)	281 (84.1)	215 (65.2)	36 (76.6)	482 (76.6)	355 (61.5)
Blood and lymphatic system disorders	156 (62.9)	37 (15.0)	240 (71.9)	46 (13.9)	36 (76.6)	432 (68.7)	83 (14.4)
Musculoskeletal and connective tissue disorders	150 (60.5)	159 (64.4)	224 (67.1)	230 (69.7)	23 (48.9)	397 (63.1)	389 (67.4)
General disorders and administration site conditions	130 (52.4)	115 (46.6)	226 (67.7)	197 (59.7)	29 (61.7)	385 (61.2)	312 (54.1)
Investigations	146 (58.9)	77 (31.2)	204 (61.1)	92 (27.9)	29 (61.7)	379 (60.3)	169 (29.3)
Skin and subcutaneous tissue disorders	117 (47.2)	83 (33.6)	209 (62.6)	126 (38.2)	25 (53.2)	351 (55.8)	209 (36.2)
Infections and infestations	113 (45.6)	91 (36.8)	187 (56.0)	162 (49.1)	26 (55.3)	326 (51.8)	253 (43.8)
Nervous system disorders	104 (41.9)	102 (41.3)	171 (51.2)	153 (46.4)	18 (38.3)	293 (46.6)	255 (44.2)
Respiratory, thoracic and mediastinal disorders	80 (32.3)	59 (23.9)	160 (47.9)	132 (40.0)	21 (44.7)	261 (41.5)	191 (33.1)
Vascular disorders	92 (37.1)	90 (36.4)	144 (43.1)	151 (45.8)	20 (42.6)	256 (40.7)	241 (41.8)
Metabolism and nutrition disorders	48 (19.4)	56 (22.7)	133 (39.8)	114 (34.5)	22 (46.8)	203 (32.3)	170 (29.5)
Psychiatric disorders	57 (23.0)	57 (23.1)	105 (31.4)	89 (27.0)	11 (23.4)	173 (27.5)	146 (25.3)
Eye disorders	36 (14.5)	17 (6.9)	90 (26.9)	39 (11.8)	13 (27.7)	139 (22.1)	56 (9.7)
Reproductive system and breast disorders	40 (16.1)	34 (13.8)	55 (16.5)	55 (16.7)	5 (10.6)	100 (15.9)	89 (15.4)
Injury, poisoning and procedural complications	20 (8.1)	18 (7.3)	54 (16.2)	38 (11.5)	8 (17.0)	82 (13.0)	56 (9.7)
Renal and urinary disorders	18 (7.3)	17 (6.9)	35 (10.5)	31 (9.4)	6 (12.8)	59 (9.4)	48 (8.3)
Cardiac disorders	22 (8.9)	9 (3.6)	34 (10.2)	23 (7.0)	3 (6.4)	59 (9.4)	32 (5.5)
Ear and labyrinth disorders	9 (3.6)	6 (2.4)	34 (10.2)	22 (6.7)	5 (10.6)	48 (7.6)	28 (4.9)
Hepatobiliary disorders	8 (3.2)	11 (4.5)	15 (4.5)	10 (3.0)	4 (8.5)	27 (4.3)	21 (3.6)
Immune system disorders	8 (3.2)	7 (2.8)	16 (4.8)	10 (3.0)	0	24 (3.8)	17 (2.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.0)	8 (3.2)	12 (3.6)	14 (4.2)	2 (4.3)	19 (3.0)	22 (3.8)
Endocrine disorders	2 (0.8)	1 (0.4)	8 (2.4)	2 (0.6)	3 (6.4)	13 (2.1)	3 (0.5)
Congenital, familial and genetic disorders	0	0	1 (0.3)	0	1 (2.1)	2 (0.3)	0

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
System organ classes are sorted in descending order of frequency in the pooled ribociclib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
Source: [SCS Study E2301-Appendix 1-Table 3-4.2]

Table 80: AEs by PT, irrespective of causality (with at least 10% incidence in pooled – ribo plus NSAI group) in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO+LET/ANA[1]	PBO+LET/ANA[1]	RIBO+LET	PBO+LET	RIBO+LET	RIBO+NSAI[1]	PBO+NSAI[1]
Preferred term	N=248	N=247	N=334	N=330	N=47	N=629	N=577
Total	**242 (97.6)**	**229 (92.7)**	**331 (99.1)**	**322 (97.6)**	**47 (100)**	**620 (98.6)**	**551 (95.5)**
Neutropenia	140 (56.5)	12 (4.9)	214 (64.1)	16 (4.8)	35 (74.5)	389 (61.8)	28 (4.9)
Nausea	78 (31.5)	50 (20.2)	178 (53.3)	101 (30.6)	24 (51.1)	280 (44.5)	151 (26.2)
Fatigue	58 (23.4)	62 (25.1)	138 (41.3)	107 (32.4)	18 (38.3)	214 (34.0)	169 (29.3)
Arthralgia	83 (33.5)	71 (28.7)	111 (33.2)	108 (32.7)	15 (31.9)	209 (33.2)	179 (31.0)
Diarrhoea	49 (19.8)	46 (18.6)	128 (38.3)	81 (24.5)	19 (40.4)	196 (31.2)	127 (22.0)
Alopecia	51 (20.6)	33 (13.4)	115 (34.4)	53 (16.1)	14 (29.8)	180 (28.6)	86 (14.9)
Hot flush	77 (31.0)	75 (30.4)	82 (24.6)	84 (25.5)	11 (23.4)	170 (27.0)	159 (27.6)
Vomiting	43 (17.3)	42 (17.0)	112 (33.5)	55 (16.7)	12 (25.5)	167 (26.6)	97 (16.8)
Neutrophil count decreased	83 (33.5)	5 (2.0)	72 (21.6)	4 (1.2)	8 (17.0)	163 (25.9)	9 (1.6)
Headache	58 (23.4)	59 (23.9)	90 (26.9)	69 (20.9)	10 (21.3)	158 (25.1)	128 (22.2)
Constipation	40 (16.1)	30 (12.1)	93 (27.8)	71 (21.5)	12 (25.5)	145 (23.1)	101 (17.5)
Back pain	45 (18.1)	44 (17.8)	81 (24.3)	67 (20.3)	12 (25.5)	138 (21.9)	111 (19.2)
Anaemia	44 (17.7)	18 (7.3)	69 (20.7)	19 (5.8)	13 (27.7)	126 (20.0)	37 (6.4)
Cough	36 (14.5)	25 (10.1)	77 (23.1)	70 (21.2)	12 (25.5)	125 (19.9)	95 (16.5)
Rash	34 (13.7)	21 (8.5)	64 (19.2)	28 (8.5)	11 (23.4)	109 (17.3)	49 (8.5)
White blood cell count decreased	34 (13.7)	3 (1.2)	63 (18.9)	7 (2.1)	8 (17.0)	105 (16.7)	10 (1.7)
Alanine aminotransferase increased	33 (13.3)	22 (8.9)	58 (17.4)	15 (4.5)	10 (21.3)	101 (16.1)	37 (6.4)
Leukopenia	41 (16.5)	5 (2.0)	52 (15.6)	9 (2.7)	5 (10.6)	98 (15.6)	14 (2.4)
Aspartate aminotransferase increased	32 (12.9)	25 (10.1)	54 (16.2)	15 (4.5)	10 (21.3)	96 (15.3)	40 (6.9)
Decreased appetite	16 (6.5)	18 (7.3)	69 (20.7)	52 (15.8)	9 (19.1)	94 (14.9)	70 (12.1)
Pyrexia	41 (16.5)	16 (6.5)	44 (13.2)	19 (5.8)	5 (10.6)	90 (14.3)	35 (6.1)
Asthenia	30 (12.1)	27 (10.9)	46 (13.8)	45 (13.6)	11 (23.4)	87 (13.8)	72 (12.5)
Pain in extremity	25 (10.1)	20 (8.1)	49 (14.7)	55 (16.7)	8 (17.0)	82 (13.0)	75 (13.0)
Stomatitis	26 (10.5)	19 (7.7)	48 (14.4)	22 (6.7)	8 (17.0)	82 (13.0)	41 (7.1)
Hypertension	16 (6.5)	19 (7.7)	64 (19.2)	61 (18.5)	1 (2.1)	81 (12.9)	80 (13.9)
Insomnia	29 (11.7)	31 (12.6)	47 (14.1)	38 (11.5)	5 (10.6)	81 (12.9)	69 (12.0)
Pruritus	23 (9.3)	10 (4.0)	50 (15.0)	21 (6.4)	8 (17.0)	81 (12.9)	31 (5.4)
Upper respiratory tract infection	32 (12.9)	23 (9.3)	44 (13.2)	40 (12.1)	5 (10.6)	81 (12.9)	63 (10.9)
Urinary tract infection	22 (8.9)	17 (6.9)	44 (13.2)	34 (10.3)	10 (21.3)	76 (12.1)	51 (8.8)
Abdominal pain	25 (10.1)	19 (7.7)	42 (12.6)	27 (8.2)	6 (12.8)	73 (11.6)	46 (8.0)
Dizziness	14 (5.6)	14 (5.7)	48 (14.4)	50 (15.2)	3 (6.4)	65 (10.3)	64 (11.1)
Dyspnoea	13 (5.2)	15 (6.1)	47 (14.1)	36 (10.9)	4 (8.5)	64 (10.2)	51 (8.8)
Musculoskeletal pain	24 (9.7)	31 (12.6)	34 (10.2)	53 (16.1)	5 (10.6)	63 (10.0)	84 (14.6)

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Preferred terms are sorted in descending order of frequency, as reported under pooled ribocilcib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
MedDRA Version 20.0 has been used for coding of adverse events.
Source: [SCS Study E2301-Appendix 1-Table 3-4.4]

Table 81: Grade 3-4 adverse events by PT, irrespective of causality (with at least a 2.0% incidence in 'Grade 3' – 'pooled ribo+NSAI') in Study E2301 (Safety set)

	Study E2301				Study A2301				Study X2107		Pooled data			
	RIBO+LET/ANA[1] N=248		PBO+LET/ANA[1] N=247		RIBO+LET N=334		PBO+LET N=330		RIBO+LET N=47		RIBO+NSAI[1] N=629		PBO+NSAI[1] N=577	
	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	**158 (63.7)**	**33 (13.3)**	**67 (27.1)**	**10 (4.0)**	**232 (69.5)**	**56 (16.8)**	**117 (35.5)**	**6 (1.8)**	**38 (80.9)**	**3 (6.4)**	**428 (68.0)**	**92 (14.6)**	**184 (31.9)**	**16 (2.8)**
Neutropenia	97 (39.1)	15 (6.0)	4 (1.6)	0	139 (41.6)	29 (8.7)	3 (0.9)	0	22 (46.8)	2 (4.3)	258 (41.0)	46 (7.3)	7 (1.2)	0
Neutrophil count decreased	58 (23.4)	11 (4.4)	2 (0.8)	1 (0.4)	53 (15.9)	3 (0.9)	1 (0.3)	0	7 (14.9)	0	118 (18.8)	14 (2.2)	3 (0.5)	1 (0.2)
WBC count decreased	19 (7.7)	0	0	0	41 (12.3)	2 (0.6)	2 (0.6)	0	5 (10.6)	0	65 (10.3)	2 (0.3)	2 (0.3)	0
Hypertension	6 (2.4)	0	7 (2.8)	0	42 (12.6)	0	42 (12.7)	0	1 (2.1)	0	49 (7.8)	0	49 (8.5)	0
ALT increased	12 (4.8)	0	3 (1.2)	0	27 (8.1)	6 (1.8)	4 (1.2)	0	2 (4.3)	0	41 (6.5)	6 (1.0)	7 (1.2)	0
Leukopenia	14 (5.6)	1 (0.4)	1 (0.4)	0	28 (8.4)	2 (0.6)	1 (0.3)	0	2 (4.3)	0	44 (7.0)	3 (0.5)	2 (0.3)	0
AST increased	9 (3.6)	0	3 (1.2)	0	17 (5.1)	3 (0.9)	4 (1.2)	0	2 (4.3)	0	28 (4.5)	3 (0.5)	7 (1.2)	0
Lymphocyte count decreased	3 (1.2)	0	1 (0.4)	0	17 (5.1)	1 (0.3)	2 (0.6)	0	1 (2.1)	0	21 (3.3)	1 (0.2)	3 (0.5)	0
Vomiting	2 (0.8)	0	0	0	12 (3.6)	0	3 (0.9)	0	0	0	14 (2.2)	0	3 (0.5)	0
Lymphopenia	6 (2.4)	1 (0.4)	1 (0.4)	0	6 (1.8)	3 (0.9)	1 (0.3)	0	2 (4.3)	0	14 (2.2)	4 (0.6)	2 (0.3)	0
Anaemia	6 (2.4)	0	3 (1.2)	0	6 (1.8)	2 (0.6)	4 (1.2)	0	0	0	12 (1.9)	2 (0.3)	7 (1.2)	0
Back pain	2 (0.8)	0	4 (1.6)	0	10 (3.0)	0	1 (0.3)	0	0	0	12 (1.9)	0	5 (0.9)	0
Fatigue	2 (0.8)	0	0	0	9 (2.7)	1 (0.3)	3 (0.9)	0	1 (2.1)	0	12 (1.9)	1 (0.2)	3 (0.5)	0
Diarrhoea	5 (2.0)	0	0	0	8 (2.4)	0	3 (0.9)	0	0	0	13 (2.1)	0	3 (0.5)	0
Hypophosphataemia	1 (0.4)	0	3 (1.2)	0	8 (2.4)	1 (0.3)	2 (0.6)	0	1 (2.1)	0	10 (1.6)	1 (0.2)	5 (0.9)	0
Nausea	0	0	0	0	8 (2.4)	0	2 (0.6)	0	1 (2.1)	0	9 (1.4)	0	2 (0.3)	0
Febrile neutropenia	6 (2.4)	0	2 (0.8)	0	3 (0.9)	1 (0.3)	0	0	0	0	9 (1.4)	1 (0.2)	2 (0.3)	0
Syncope	0	0	0	0	8 (2.4)	0	6 (1.8)	0	0	0	8 (1.3)	0	6 (1.0)	0

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Preferred terms are sorted in descending order of frequency in the all grades column, as reported in pooled ribociclib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
MedDRA Version 20.0 has been used for coding of adverse events..
Source: [SCS Study E2301-Appendix 1-Table 3-4.2]

Serious adverse event (SAEs)

Table 82: SAEs by PT, irrespective of causality (with an incidence of at least 0.5% in - 'pooled ribo + NSAI') in Study E2301 - (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO+ LET/ANA[1] N=248	PBO+ LET/ANA[1] N=247	RIBO+ LET N=334	PBO+ LET N=330	RIBO+ LET N=47	RIBO+ NSAI[1] N=629	PBO+ NSAI[1] N=577
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total	**42 (16.9)**	**33 (13.4)**	**85 (25.4)**	**51 (15.5)**	**10 (21.3)**	**137 (21.8)**	**84 (14.6)**
Abdominal pain	3 (1.2)	0	5 (1.5)	0	0	8 (1.3)	0
Dyspnoea	3 (1.2)	2 (0.8)	5 (1.5)	2 (0.6)	0	8 (1.3)	4 (0.7)
Pneumonia	0	1 (0.4)	6 (1.8)	3 (0.9)	1 (2.1)	7 (1.1)	4 (0.7)
Vomiting	1 (0.4)	1 (0.4)	5 (1.5)	2 (0.6)	0	6 (1.0)	3 (0.5)
Anaemia	2 (0.8)	0	4 (1.2)	1 (0.3)	0	6 (1.0)	1 (0.2)
Febrile neutropenia	3 (1.2)	1 (0.4)	3 (0.9)	0	0	6 (1.0)	1 (0.2)
Back pain	3 (1.2)	1 (0.4)	3 (0.9)	1 (0.3)	0	6 (1.0)	2 (0.3)
Constipation	0	0	4 (1.2)	0	1 (2.1)	5 (0.8)	0
ALT increased	1 (0.4)	1 (0.4)	4 (1.2)	0	0	5 (0.8)	1 (0.2)
Pleural effusion	2 (0.8)	4 (1.6)	3 (0.9)	4 (1.2)	0	5 (0.8)	8 (1.4)
Urinary tract infection	0	0	3 (0.9)	0	1 (2.1)	4 (0.6)	0
Diarrhoea	2 (0.8)	1 (0.4)	2 (0.6)	0	0	4 (0.6)	1 (0.2)
Nausea	0	1 (0.4)	4 (1.2)	2 (0.6)	0	4 (0.6)	3 (0.5)
Neutropenia	1 (0.4)	0	3 (0.9)	0	0	4 (0.6)	0
General physical health deterioration	0	0	4 (1.2)	1 (0.3)	0	4 (0.6)	1 (0.2)
Pyrexia	2 (0.8)	2 (0.8)	1 (0.3)	0	1 (2.1)	4 (0.6)	2 (0.3)
Drug-induced liver injury	4 (1.6)	1 (0.4)	0	0	0	4 (0.6)	1 (0.2)
AST increased	1 (0.4)	1 (0.4)	3 (0.9)	0	0	4 (0.6)	1 (0.2)
Dehydration	0	0	4 (1.2)	2 (0.6)	0	4 (0.6)	2 (0.3)
Dizziness	0	0	4 (1.2)	1 (0.3)	0	4 (0.6)	1 (0.2)
Pulmonary embolism	1 (0.4)	1 (0.4)	3 (0.9)	1 (0.3)	0	4 (0.6)	2 (0.3)
Hepatotoxicity	0	1 (0.4)	3 (0.9)	0	0	3 (0.5)	1 (0.2)
Lung infection	2 (0.8)	0	1 (0.3)	0	0	3 (0.5)	0
Sepsis	0	0	3 (0.9)	0	0	3 (0.5)	0
Syncope	0	0	3 (0.9)	2 (0.6)	0	3 (0.5)	2 (0.3)

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Preferred terms are sorted in descending order of frequency, as reported in pooled ribociclib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
MedDRA Version 20.0 has been used for coding of adverse events.
Source: [SCS Study E2301-Appendix 1-Table 3-4.8]

Deaths

Table 83: Deaths while on treatment, by preferred terms in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO+ LET/ANA[1]	PBO+ LET/ANA[1]	RIBO+ LET	PBO+ LET	RIBO+ LET	RIBO+ NSAI[1]	PBO+ NSAI[1]
Primary reason for death	**N=248**	**N=247**	**N=334**	**N=330**	**N=47**	**N=629**	**N=577**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
On-treatment deaths	**1 (0.4)**	**5 (2.0)**	**7 (2.1)**	**3 (0.9)**	**0**	**8 (1.3)**	**8 (1.4)**
Study indication	1 (0.4)	5 (2.0)	2 (0.6)	2 (0.6)	0	3 (0.5)	7 (1.2)
Other	0	0	5 (1.5)	1 (0.3)	0	5 (0.8)	1 (0.2)
Acute respiratory failure	0	0	2 (0.6)	0	0	2 (0.3)	0
Death	0	0	1 (0.3)	0	0	1 (0.2)	0
Pneumonia	0	0	1 (0.3)	0	0	1 (0.2)	0
Sudden death	0	0	1 (0.3)	0	0	1 (0.2)	0
Subdural haematoma	0	0	0	1 (0.3)	0	0	1 (0.2)

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Source: [SCS Study E2301-Appendix 1-Table 3-4.6]

AEs of Special Interest (AESIs)

QT interval prolongation and QTc

The proportion of patients with 'QT interval prolongation' events was higher in the test arm (9.3 %) as compared to the control arm (3.2 %). Most events were Grade 1 or 2. Grade 3 events were reported in 1.2 % of patients in test arm whilst none in the control arm. There were no Grade 4 events reported. Dose adjustments or interruptions were required 3.2 % of patients, and all were due to the AE of electrocardiogram QT prolonged. Syncope was reported in one patient (0.4%) with no action taken and the event resolved. One patient (0.4 %) in each arm discontinued study treatment due to event of ECG QT prolonged. QTcF prolongation was not associated with cardiac SAEs or arrhythmias and there were no events of cardiac arrest, sudden death, or Torsade de Pointes reported.

Hepatobiliary toxicity events

The proportion of patients with hepatobiliary toxicity events were similar between the test and control arm (21.0 % vs. 20.2%) and likewise the proportion of patients with grade 3 (7.3 % vs. 6.5 %) and grade 4 events (0.8 % in both the treatment arms) were also similar. The most frequently reported events included: ALT increased (13.3 % vs. 8.9 %) and AST increased (12.9 % vs. 10.1 %). Dose interruptions or adjustments were required for 6.5% of patients in the test arm vs. 5.3% in the control arm, primarily due to ALT increased and AST increased.

Eleven patients (4.4 %) in the test arm and three patients (1.2%) in the control arm discontinued study treatment due to hepatobiliary events. Notably, three patients and one patient in the respective arms discontinued treatment due to event of potential drug-induced liver injury (DILI). Based on the laboratory data, considering the biochemical Hy's law criteria (AST/ALT >3.0x ULN and total bilirunin (TBL) >2.0xULN and ALP <2xULN) at any time during the treatment period, 3 cases (1 in the test arm and 2 in the control arm) were identified. Upon medical review, it was concluded that confounding factors were present, thus not meeting the three criteria needed to qualify for Hy's law.

Laboratory findings

In the E2301 study, post-baseline haematological laboratory abnormalities of any grade occurred in a higher proportion of patients in the test arm as compared to the control arm. Most were of grade 1 or2 in both

treatment arms. The most frequent grade 3 in the test arm as compared to the control arm (≥10% difference) were decreased absolute neutrophil count (+51.2 %) and decreased leukocyte count (+33.9 %). Decreased neutrophils (9.3 %) were the most frequent grade 4 abnormality in the test arm.

In terms of post-baseline biochemical laboratory abnormalities (any grade) occurred in similar proportions of patients in the both arms. Elevations in ALT (5.6 %) and GGT (5.2 %) were frequent grade 3 abnormalities whilst grade 4 was primarily due to elevated GGT (1.6%). Hypercholesterolemia (predominantly grade 1 or 2) was noted in >50% of patients in both the treatment groups. Of note, there were 36.2 % and 27.9 % of patients who had grade 1 or 2 cholesterol at baseline in the in the respective arms. Post baseline findings were comparable between the two arms (60.5% and 55.1% respectively).

Safety in special populations

The E2301 study only enrolled female patients with a median age of 43 years (range 25 to 58 years) and all the patients were aged <65 years. Safety in the elderly population has already been assessed in the registrational study A2301. In the ribociclib group, the incidence of AEs was generally similar for patients in different age subgroups (<40 years and ≥ 40 years). Differences (≥10% across the age groups) were observed for few events including: back pain (+10.9 %) and diarrhoea (+10.4 %) which were more frequently reported amongst patients <40 years compared to≥40 years.

In terms of race, about 56 % were Caucasian whilst Asian about 34 %. The incidence of AESIs in the test arm was generally comparable across the two subpopulations. 'Infections' events and 'leukopenia' events were more prominent in Caucasians (12.8 % and 29.4 % respectively) compared to Asian subpopulation (9.2 % and 22.0 % respectively).

Discontinuation due to adverse events

Table 84: AEs leading to discontinuation by PT, irrespective of causality (with an incidence of at least 0.5% - 'ribo+NSAI' group in pooled data) in Study E2301 (Safety set)

	Study E2301		Study A2301		Study X2107	Pooled data	
	RIBO+ LET/ANA[1] N=248	PBO+ LET/ANA[1] N=247	RIBO+ LET N=334	PBO+ LET N=330	RIBO+ LET N=47	RIBO+ NSAI[1] N=629	PBO+ NSAI[1] N=577
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**16 (6.5)**	**8 (3.2)**	**56 (16.8)**	**13 (3.9)**	**2 (4.3)**	**74 (11.8)**	**21 (3.6)**
ALT increased	6 (2.4)	2 (0.8)	15 (4.5)	1 (0.3)	2 (4.3)	23 (3.7)	3 (0.5)
AST increased	4 (1.6)	2 (0.8)	9 (2.7)	2 (0.6)	0	13 (2.1)	4 (0.7)
Vomiting	0	0	8 (2.4)	0	0	8 (1.3)	0
Drug-induced liver injury	3 (1.2)	1 (0.4)	0	0	0	3 (0.5)	1 (0.2)
Neutropenia	1 (0.4)	0	3 (0.9)	0	0	4 (0.6)	0
Nausea	0	0	3 (0.9)	0	0	3 (0.5)	0

LET=letrozole; ANA=anastrazole; NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1]For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Peferred terms are sorted in descending order of frequency in pooled ribociclib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
MedDRA Version 20.0 has been used for coding of adverse events.
Source: [SCS Study E2301-Appendix 1-Table 3-4.10]

Comparison of AEs between clinical trials

Table 85: Comparison of safety profiles between E2301, A2301 (initial registrational study) and F2301

Study	Any AEs (%)	Grade 3 or 4 (%)	SAEs (%)	Discont due to AEs (%)	Dose interrupt due to AEs (%)	Dose adjust due to AEs (%)	All deaths (%)	Most common AEs with at least 10% incidence (%)
E2301 Ribo+AI +LHRH N=248 Pre/peri	97.6	77.0	16.9	6.5	72.6	33.5	12.1	Neutropenia: 56.5 Neutrophil count decreased: 33.5 Arthralgia: 33.5 Nausea: 31.5 Fatigue: 23.4
A2301 Ribo+AI N=334 postmeno	99.1	86.2	25.4	16.8	75.1	47.9	15.0	Neutropenia: 64.1 Nausea: 53.3 Fatigue: 41.3 Diarrhoea: 38.3 Vomiting: 33.5 Arthralgia: 33.2
F2301 Ribo+fulv N=483	99.2	Gr 3: 64.0 Gr 4: 14.3	28.6	17.2	68.5	33.1	14.5	Neutropenia: 55.9 Nausea: 45.3 Fatigue: 31.5 Diarrhoea: 29.0 Vomiting: 26.7

Post marketing experience

The MAH performed a literature search to assess any new information in the public domain regarding data on safety with ribociclib during the reporting period of 22-Aug-2017 to the 21-Feb-2018. Ovid Medline, Embase, and Biosis Previews were searched with criteria inclusive of pregnancy outcomes (including termination) with no adverse outcomes, use in pediatric populations, compassionate supply, named patient use, lack of efficacy, asymptomatic overdose, abuse or misuse, medication error where no AEs occurred, “near misses”, and important nonclinical safety results. No new or significant safety findings were identified that impacted the current benefit-risk assessment of ribociclib.

With regards to overdose, there is only limited experience with reported cases of overdosage with Kisqali. In the event of an overdose, symptoms such as nausea and vomiting may occur. In addition, haematological (e.g. neutropenia, thrombocytopenia) toxicity and possible QTc prolongation may occur. General supportive care should be initiated in all cases of overdosage as necessary.

Adverse drug reactions

The overall safety evaluation of Kisqali was based on the pooled dataset from 1,065 patients who received Kisqali in combination with endocrine therapy (N=582 in combination with an aromatase inhibitor and N=483 in combination with fulvestrant) and who were included in the randomised, double blind, placebo

controlled phase III clinical studies (MONALEESA 2, MONALEESA 7 NSAI subgroup and MONALEESA 3) in HR positive, HER2 negative advanced or metastatic breast cancer. The median duration of exposure to Kisqali treatment across the pooled phase III studies dataset was 16.5 months, with 61.7% patients exposed ≥12 months.

Dose reduction due to adverse events, regardless of causality, occurred in 37.3% of patients receiving Kisqali in the phase III clinical studies regardless of the combination and permanent discontinuation was reported in 7.0% of patients receiving Kisqali and any combination in the phase III clinical studies.

Table 86: Adverse drug reactions based on pooled data set from 3 phase III clinical studies (Pooled set)

Adverse drug reaction	RIBO+ET N=1065		PBO+ET N=818		Freq. category
	Frequency n (%)	Grade 3 or 4 n (%)	Frequency n (%)	Grade 3 or 4 n (%)	
Total	**1052 (98.8)**	**857 (80.5)**	**782 (95.6)**	**271 (33.1)**	
Neutropenia	785 (73.7)	624 (58.6)	41 (5.0)	11 (1.3)	Very common
Nausea	475 (44.6)	15 (1.4)	219 (26.8)	4 (0.5)	Very common
Infections[1]	434 (40.8)	41 (3.8)	245 (30.0)	8 (1.0)	Very common
Fatigue	348 (32.7)	20 (1.9)	249 (30.4)	4 (0.5)	Very common
Diarrhoea	317 (29.8)	16 (1.5)	176 (21.5)	5 (0.6)	Very common
Leukopenia	314 (29.5)	165 (15.5)	24 (2.9)	4 (0.5)	Very common
Vomiting	284 (26.7)	21 (2.0)	128 (15.6)	3 (0.4)	Very common
Alopecia	256 (24.0)	0	97 (11.9)	0	Very common
Headache	253 (23.8)	5 (0.5)	177 (21.6)	4 (0.5)	Very common
Constipation	253 (23.8)	8 (0.8)	129 (15.8)	0	Very common
Rash[2]	227 (21.3)	10 (0.9)	70 (8.6)	0	Very common
Cough	218 (20.5)	0	132 (16.1)	0	Very common
Back pain	211 (19.8)	20 (1.9)	153 (18.7)	7 (0.9)	Very common
Anaemia	200 (18.8)	30 (2.8)	51 (6.2)	12 (1.5)	Very common
Abnormal liver function[3] tests	184 (17.3)	93 (8.7)	66 (8.1)	16 (2.0)	Very common
Abdominal pain[4]	182 (17.1)	14 (1.3)	107 (13.1)	4 (0.5)	Very common
Pruritus	177 (16.6)	3 (0.3)	48 (5.9)	0	Very common
Decreased appetite	163 (15.3)	6 (0.6)	101 (12.3)	1 (0.1)	Very common
Oedema peripheral	147 (13.8)	1 (0.1)	71 (8.7)	0	Very common
Asthenia	145 (13.6)	7 (0.7)	103 (12.6)	3 (0.4)	Very common
Pyrexia	139 (13.1)	4 (0.4)	52 (6.4)	0	Very common
Dyspnoea	132 (12.4)	15 (1.4)	81 (9.9)	7 (0.9)	Very common
Dizziness	125 (11.7)	1 (0.1)	83 (10.1)	0	Very common
Stomatitis	122 (11.5)	3 (0.3)	53 (6.5)	1 (0.1)	Very common
Lymphopenia	95 (8.9)	56 (5.3)	18 (2.2)	5 (0.6)	Common
Thrombocytopenia	95 (8.9)	8 (0.8)	11 (1.3)	1 (0.1)	Common
Dyspepsia	88 (8.3)	1 (0.1)	35 (4.3)	0	Common
Dry skin	88 (8.3)	0	18 (2.2)	0	Common
Dry mouth	74 (6.9)	1 (0.1)	44 (5.4)	0	Common
Dysgeusia	71 (6.7)	1 (0.1)	36 (4.4)	0	Common
Electrocardiogram QT prolonged	69 (6.5)	13 (1.2)	13 (1.6)	2 (0.2)	Common
Oropharyngeal pain	67 (6.3)	0	33 (4.0)	0	Common
Blood creatinine increased	67 (6.3)	4 (0.4)	15 (1.8)	0	Common
Lacrimation increased	59 (5.5)	0	9 (1.1)	0	Common

Adverse drug reaction	RIBO+ET N=1065		PBO+ET N=818		Freq. category
	Frequency n (%)	Grade 3 or 4 n (%)	Frequency n (%)	Grade 3 or 4 n (%)	
Dry eye	54 (5.1)	0	18 (2.2)	0	Common
Vertigo	46 (4.3)	1 (0.1)	10 (1.2)	0	Common
Hypocalcaemia	45 (4.2)	11 (1.0)	14 (1.7)	0	Common
Erythema	43 (4.0)	2 (0.2)	8 (1.0)	0	Common
Hypophosphataemia	34 (3.2)	22 (2.1)	11 (1.3)	7 (0.9)	Common
Hypokalaemia	33 (3.1)	12 (1.1)	21 (2.6)	5 (0.6)	Common
Syncope	19 (1.8)	12 (1.1)	9 (1.1)	7 (0.9)	Common
Hepatotoxicity[5]	19 (1.8)	15 (1.4)	7 (0.9)	4 (0.5)	Common
Vitiligo	16 (1.5)	0	0	0	Common
Febrile neutropenia	15 (1.4)	15 (1.4)	2 (0.2)	2 (0.2)	Common

[1] Infections: Urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (<1%).

[2] Rash: rash, rash maculopapular, rash pruritic.

[3] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

[4]Abdominal pain: Abdominal pain, abdominal pain upper.

[5] Hepatotoxicity: hepatocellular injury, drug induced liver injury, hepatotoxicity, hepatic failure, autoimmune hepatitis (single case).

- For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.

Numbers (n) represent counts of subjects.

MedDRA version 20.1, CTCAE version 4.03.

Frequency category is based on the following convention: very common (>=1/10); common (>=1/100 to <1/10); uncommon (>=1/1,000 to <1/100); rare (>=1/10,000 to <1/1,000); very rare (<1/10,000)

Source: [SCS Study F2301-Appendix 4-Table 10-1]

New ADRs which met the ADR screening and medical judgement criteria were included: infections (+10.8%), including: urinary tract infections, respiratory tract infections (including upper and lower), gastroenteritis and sepsis (<1%); cough (+4.3%); dry skin (+6.1%); vertigo (+3.1%); oropharyngeal pain (+2.3%); rash pruritic (+1.1%; under umbrella term rash: +12.8%); abdominal pain upper (+2.1%; under umbrella term abdominal pain: +4.0%); vitiligo (+1.5%); dizziness (+1.6%); dry mouth (+1.6%).

Three ADRs currently listed in the ribociclib approved label (Epistaxis, Weight decreased and Insomnia) have been removed based on the results of the assessment following the methodology described above:

- Epistaxis did not meet any ADR screening criteria, showing a below threshold imbalance between ribociclib and placebo (+1.20%), no grade 3 and 4 events, and no events leading to discontinuation. In addition, a comprehensive evaluation of haemorrhage and possible association to thrombocytopenia was performed in the Argus safety database and did not reveal any noteworthy cases.

- Weight decreased did not meet any ADR screening criteria, showing a below threshold imbalance between ribociclib and placebo (+1.30%); few grade 3 and 4 events were reported in both arms; with only one event leading to discontinuation in the ribociclib arm. The evaluation of the cases reported to the safety database showed few cases of Weight decreased (6 non-serious, and 2 serious); assessed by the MAH as unlikely related to ribociclib due to presence of confounders.

- Insomnia showed a discrete imbalance between ribociclib and placebo (+1.0%), with a negative risk difference in study E2301 (more frequent in placebo); no events leading to discontinuation were reported; in Argus, 9 cases of Insomnia were reported, all nonserious, 7 of which were considered not assessable by both the reporters and the MAH.

Considering four cases were reported as drug induced liver injury (DILI) in the ribociclib + AI arm (whereof two considered Grade 3) in the E2301 study, the frequency of this ADR has also been included in the SmPC. Based on the available data from the 3 pivotal Kisqali registration studies (MONALEESA-2, -3, and -7) the frequency category of “uncommon” (n=5 [0.5%]; N= 1065) has been included.

<u>Description of selected adverse drug reactions</u>

Neutropenia

Among the patients who had grade 2, 3 or 4 neutropenia, the median time to onset was 16 days, for those patients who had an event. The median time to resolution of grade ≥3 (to normalisation or grade <3) was 12 days in the Kisqali plus any combination arms following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in about 1.4% of patients exposed to Kisqali in the phase III studies.

Hepatobiliary toxicity

In the phase III clinical studies, hepatobiliary toxicity events occurred in a higher proportion of patients in the Kisqali plus any combination arms compared with the placebo plus any combination arms (23.2% versus 16.5%, respectively), with more grade 3/4 adverse events reported in the patients treated with Kisqali plus any combination (11.4% versus 5.4%, respectively). Increases in transaminases were observed. Grade 3 or 4 increases in ALT (9.7% versus 1.5%) and AST (6.7% versus 2.1%) were reported in the Kisqali and placebo arms, respectively. Concurrent elevations in ALT or AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301 [MONALEESA-2], whose levels recovered to normal within 154 days and 2 patients in Study F2301 [MONALEESA-3], whose levels recovered to normal in 121 and 532 days, respectively, after discontinuation of Kisqali. There were no such cases reported in Study E2301 (MONALEESA-7).

Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 10.4% of Kisqali plus any combination treated patients, primarily due to ALT increased (6.9%) and/or AST increased (6.1%). Discontinuation of treatment with Kisqali plus any combination due to abnormal liver function tests or hepatotoxicity occurred in 2.3% and 0.4% of patients respectively.

In the phase III clinical studies, 83.2% (89/107) of grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment. Among the patients who had grade 3 or 4 ALT/AST elevation, the median time to onset was 85 days for the Kisqali plus any combination arms. The median time to resolution (to normalisation or grade ≤2) was 22 days in the Kisqali plus any combination arms.

QT prolongation

In the phase III clinical studies 8.4% of patients in the Kisqali plus aromatase inhibitor or fulvestrant arms and 3.2% in the placebo plus aromatase inhibitor or fulvestrant arms had at least one event of QT interval prolongation (including ECG QT prolonged and syncope). Review of ECG data showed 14 patients (1.3%) had >500 msec post-baseline QTcF value, and 59 patients (5.6%) had a >60 msec increase from baseline in QTcF intervals. There were no reported cases of torsade de pointes. Dose interruptions/adjustments were reported in 2.3% of Kisqali plus aromatase inhibitor or fulvestrant treated patients due to electrocardiogram QT prolonged and syncope.

The analysis of ECG data showed 52 patients (4.9%) and 11 patients (1.4%) with at least one >480 msec post-baseline QTcF for the Kisqali plus aromatase inhibitor or fulvestrant arms and the placebo plus aromatase inhibitor or fulvestrant arms, respectively. Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was 15 days regardless of the combination and these changes were reversible with dose interruption and/or dose reduction.

2.5.1. Discussion on clinical safety

Ribociclib in combination with fulvestrant

The study F2301 (MONALEESA 3) enrolled postmenopausal women treated with ribociclib + fulvestrant (N=483) vs. placebo + fulvestrant (N=241) as 1st or 2nd line (after only one line of prior endocrine

treatment). Male breast cancer patients were also eligible but none were enrolled. The safety profiles between ribociclib + AI and ribociclib + fulvestrant are considered similar (Table 85).

Median duration of exposure to ribociclib + fulvestrant was 16 months as compared to 12 months for the control arm. About 58 % of the patients were exposed to the ribociclib + fulvestrant combination for 12 months or more with 39 % for ≥ 18 months meaning that there is an acceptable level of available long term safety data for the combination. The corresponding data for the control arm is 49 % and 31 %. It is considered that a sufficient number of patients have been exposed to ribociclib in combination with fulvestrant.

Median relative dose intensity (RDI) was 92 % (22.7 to 133.3) in patients receiving ribociclib + fulvestrant compared with 100 % (56.6 to 118.6) in patients receiving placebo + fulvestrant.

Dose reductions (overall 37.9 %), dose interruptions (75.4 %), and dosing delays (51.3 %) were in general due to AEs (33.1 %, 68.5 % and 44.9 % respectively). It is noted that whilst dose reductions were not required in the majority of patients in the test arm (62.1 %), dose interruptions and delays were commonly reported. Median time to first dose reduction was 13.0 weeks in patients who received ribociclib + fulvestrant vs. 21 weeks in the control arm and median time to first dose interruption was 4 weeks vs. 12 weeks in the respective arms. In the control arm, the majority did not require any dose reduction, dose interruption or dose delay.

In terms of primary reason for end of treatment, progressive disease was the primary reason in 40 % and 59 % in the test and control arm respectively while a low proportion was due to AEs (8.5 % and 4.1 respectively).

The majority of AEs were considered drug related. The SOCs where a higher proportion of patients receiving ribociclib + fulvestrant reported events with ≥ 10% difference relative to placebo included: Blood and lymphatic disorders (+54.0 %); Skin and subcutaneous tissue disorders (+30.8 %); Investigations (+26.9 %); Gastrointestinal disorders (+18.9 %), Infections and infestations (+13.8 %) and Eye disorders (+11.4 %).

Overall, grade 3 and grade 4 events were observed at a higher proportion with ribociclib + fulvestrant (64.0 % and 14.3 %, respectively) vs. the control arm (25.3 % vs. 4.1 %, respectively). A higher proportion of patients in the experimental arm reported grade 3/4 events by SOC (with ≥ 5% difference relative to matching placebo) that included: Blood and lymphatic disorders (+43.7 %) and Investigations (+24.6 %).

The most common AEs (≥30%) irrespective of causal relationship reported with the ribociclib + fulvestrant combination were neutropenia, nausea and fatigue. It is recognised that overall, most events were of Grade 1 or 2. AEs where a higher proportion of patients receiving ribociclib + fulvestrant reported events (with ≥ 10% difference relative the control arm) included e.g. neutropenia (+55.1%), , nausea (+17.1%), vomiting (+13.8%), constipation (+13.2%), rash (+12.6%), and anaemia (+11.2%).

Grade 3/4 AEs irrespective of causal relationship were reported at a higher proportion in the test arm (78.3%) vs. the control arm (29.5 %). By grade, grade 3 and grade 4 events were observed at a higher proportion in the test arm (64.0 % and 14.3 % respectively) as compared to the control (25.3 % and 4.1 % respectively). Of these, grade 3 AEs with ribociclib + fulvestrant treatment reported in ≥5 % of patients included e.g. neutropenia (36.6 %) and increased ALT (6.6 %) vs. grade 4 AE neutropenia (5.8 %).

A higher proportion of SAEs was observed in the ribociclib + fulvestrant combination arm (28.6%) as compared to the control arm (16.6%). Pneumonia was the most frequent SAE in 9 patients (1.9 %) in the experimental arm.

The proportion of on-treatment deaths (defined as deaths up to 30 days after last dose of study treatment) was comparable between the treatment arms (2.7 % in the experimental arm vs. 3.3% in the control arm). The majority was due to the disease under study, in six cases in the ribociclib + fulvestrant arm death was

associated with AEs. None raised any immediate concern. According to the narratives, there was no evidence of any negative effect on QT in association the either the case of cardiac failure or the case with ventricular arrhythmia.

QT interval prolongation was observed at a higher proportion with the ribociclib and fulvestrant combination (7.7%) as compared to the control arm (2.1%). QT interval prolongation is reflected in sections 4.2, 4.4 and 4.8 in the Kisqali SmPC in addition to being adjudicated as an important identified risk in the safety specification and thus considered adequately covered in the SmPC.

Hepatobiliary toxicity is reflected in sections 4.2, 4.4 and 4.8 in the Kisqali SmPC in addition to being adjudicated as an important identified risk in the safety specification thus considered adequately covered. Four cases were reported as drug induced liver injury (DILI) in the ribociclib + AI arm in the E2301 study whilst one in the ribociclib + fulvestrant arm in the F2301 study. The current presentation of hepatic safety information in section 4.8 includes hepatotoxicity as an umbrella term with an explanatory footnote including other relevant PTs including DILI (with frequency uncommon). This is considered adequate.

No additional safety concerns were raised in the elderly subgroup. No overall differences in safety of Kisqali were observed between these patients and younger patients (see SmPC section 4.2).

Ribociclib in combination with an AI

Whereas the registrational study A2301 (MONALEESA 2) studied ribociclib in combination with an AI in a population of postmenopausal women, the E2301 study (MONALEESA 7) is investigating the combination in pre-/ peri-menopausal women (with the addition of goserelin).

The dossier included also data from a treatment arm with ribociclib in combination with tamoxifen. Due to the propensity for QT prolongation associated with both these drugs, an indication for this combination has not been pursued and consequently an assessment of the safety profile for this combination has not been carried out. The risk of QT prolongation with concomitant treatment with ribociclib and tamoxifen is considered adequately reflected in the SmPC (see SmPC 4.4, 4.5 and 5.1).

In study E2301, median duration of exposure to ribociclib + AI was 15.1 months as compared to 12.8 months for the control arm. About 67 % of the patients were exposed to the ribociclib + AI combination for 12 months or more with 32 % for ≥ 18 months meaning that there is (as with the F2301 study) an acceptable level of available long term safety data for the experimental combination. The corresponding data for the control arm is 51 % and 24 %. Overall, in regard to long term safety, it is considered that a sufficient number of patients have been exposed to ribociclib in combination with an AI and in combination with fulvestrant (see above, study F2301) providing sufficient data for a reasonable characterization of the safety profile in the long term perspective.

Dose reductions (overall 37.0 %), dose interruptions (78.0 %), and dosing delays (58.9 %) were in general due to AEs (33. 3 %, 69.9 % and 53.7 % respectively). As observed in the F2301 study dose reductions were not required in the majority of patients in the test arm (63.0 %), however dose interruptions and delays were commonly reported. The median time to first dose reduction of ribociclib was ~ 10 weeks. These observations are in line with the findings in the F2301 study.

There were no major differences in the safety profile as identified in the E2301 study and the one characterized in the original A2301 study with the exception that there were overall higher proportions of AEs, by severity and SAEs reported in the latter which is likely attributed to the age differences in the population studied in the respective studies (median 43 and 62 years of age in E2301 and A2301 respectively). The majority of all AEs including those leading to dose adjustments in the experimental arm in study E2301 were considered drug related.

AEs were experienced by almost all in the respective arms (97.6% and 92.7% in the test and control arm respectively). The most frequently reported AEs regardless of study treatment relationship by SOC in the

test arm (in ≥50% of patients) were gastrointestinal disorders (66.5%), blood and lymphatic system disorders (62.9%), musculoskeletal and connective tissue disorders (60.5%), investigations (58.9%) and general disorders and administration site conditions (52.4%). Compared to the registrational A2301 study (postmenopausal women), there was a decrease in proportions of reports all through the SOCs.

The proportion of most of the AEs was comparable between the E2301 and A2301 studies. Differences were noted for the following AEs (reported less frequently in the E2301): nausea (31.5 % vs. 53.3 %), fatigue (23.4 % vs. 41.3 %), diarrhoea (19.8 % vs. 38.3 %), alopecia (20.6 % vs. 34.4 %), vomiting (17.3 % vs. 33.5 %), constipation (16.1 % vs. 27.8 %), and decreased appetite (6.5 % vs. 20.7 %).

The majority of patients (77.0 %) in the test arm had grade 3/4 AE (63.7 % and 13.3 %, grade 3 and grade 4 respectively). Grade 3/4 events were reported in 31.2 % in the placebo group (27.1 % and 4.0 %, grade 3 and grade 4 respectively). The most frequent grade 3 AEs (with incidence ≥ 20 %) in the test arm were neutropenia (39.1 %) and decreased neutrophil count (23.4 %). The incidence of grade 3/4 AEs in ribociclib exposed patients is essentially similar between the E2301 and A2301 studies.

The proportion of patients with SAEs was essentially similar between the experimental (16.9 %) and the control arm (13.4 %) in the E2301 study. None of the SAEs were reported in ≥ 2% of patients. In the test arm, drug-induced liver injury (4 patients, 1.6 %) and abdominal pain, dyspnea, febrile neutropenia, and back pain (each reported in 3 patients, 1.2 %) were the most commonly occurring SAEs. SAEs suspected to be drug related were reported in 4.8 % of patients in the ribociclib containing arm which included drug-induced liver injury (1.6 %) and febrile neutropenia (1.2 %).

As of the data cut-off date, a total of 66 deaths had occurred: 30 (12.1 %) in the test arm and 36 (14.6 %) in the control arm. Most of these deaths in both treatment groups (10.9 % and (12.6 % in the test arm and control respectively) were attributed to the study indication or underlying malignancy.

On-treatment deaths (defined as deaths occurring during study and within 30 days of the last dose of study treatment) were reported for six patients: one patient (0.4 %) in the experimental arm and five patients (2.0 %) in the control arm. All six cases were attributed to disease progression.

The proportion of patients with 'QT interval prolongation' events was higher in the test arm (9.3 %) as compared to the control arm (3.2 %). QT interval prolongation is reflected in the SmPC and included in the RMP as discussed above. As part of this application, the MAH also presented safety data in combination with tamoxifen. The observed mean QTcF increase from baseline was approximately 10 msec higher in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup, suggesting that tamoxifen alone had a QTcF prolongation effect which can contribute to the QTcF values observed in the Kisqali plus tamoxifen group. In the placebo arm, a QTcF interval increase of >60 msec from baseline occurred in 6/90 (6.7%) patients receiving tamoxifen and in no patients receiving a NSAI. A QTcF interval increase of >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a NSAI. Kisqali is not recommended to be used in combination with tamoxifen (see SmPC section 4.8).

There were four cases of drug induced liver injury (DILI) reported in the ribociclib + AI arm. Hepatobiliary toxicity is reflected in sections 4.2, 4.4 and 4.8 in the Kisqali SmPC including DILI in section 4.8 with the frequency uncommon.

The proportion of study drug discontinuations due to AEs in ribociclib exposed patients in the E2301 study was low (6.5 %). The treatment discontinuation rate due to AEs was higher in the A2301study (16.8 %) as compared to the E2301 study with a higher proportion of individual events.

Section 4.8 of the SmPC has been revised to reflect updated frequencies from the pooled dataset from the three pivotal phase III clinical studies (study A2301, study E2301 and study F2301). New ADRs which met the ADR screening and medical judgement criteria were included: infections, cough, dry skin, vertigo,

oropharyngeal pain, rash pruritic, abdominal pain upper, vitiligo, dizziness and dry mouth. Three ADRs currently listed in the ribociclib approved label (Epistaxis, Weight decreased and Insomnia) have been removed based on the results of the assessment. This is considered acceptable.

There are no new safety concerns or signals identified in either the E2301 or the F2301 study warranting a change of the RMP.

2.5.2. Conclusions on clinical safety

There were no new safety signals or concerns observed in the safety datebase from studies E2301 and F2301. The safety profile in study E2301 of ribociclib in combination with an AI in a population of pre/perimenopausal women is similar to study A2301 performed in postmenopausal women. In addition, the safety profile is in line with the safety observed with ribociclib in combination with fulvestrant, suggesting a similar safety profile of ribociclib regardless of the choice of accompanying endocrine therapy. The important safety concerns have been previously characterised with the main concerns with ribociclib being myelosuppression (primarily neutropenia), hepatobiliary toxicity and QT interval prolongation. These are considered to be adequately reflected in the SmPC as well as covered in the RMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP adopted the risk management plan for Kisqali version 3.0, dated 14 November 2018, with the following content:

Safety concerns

Table 87: Summary of the safety concerns

Important identified risks	Myelosuppression Hepatobiliary toxicity QT interval prolongation Reproductive toxicity
Important potential risks	Renal toxicity
Missing information	Safety in Japanese patients
	Safety in male patients with breast cancer
	Long-term use

Pharmacovigilance plan

Table 88: Ongoing and planned additional pharmacovigilance activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Study CLEE011A2301 (MONALEESA-2) : Is an ongoing randomized double-blind, placebo-controlled Phase III study of ribociclib in combination with letrozole for the treatment of postmenopausal women with HR+, HER2-negative advanced breast cancer who received no prior therapy for advanced disease	To compare Progression Free Survival (PFS) between ribociclib in combination with letrozole to placebo plus letrozole among postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for their advanced breast cancer.	Long term use	Final report with Overall Survival (OS) analysis	Q4-2021

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Myelosuppression	Section 4.2, Section 4.4 and Section 4.8 of the SmPC	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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for adverse reaction Additional pharmacovigilance activities: None
Reproductive Toxicity	Section 4.4, Section 4.6 and Section 5.3 of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	the SmPC	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
Safety in male patients with breast cancer	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
Long-term use	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: Study CLEE011A2301 (MONALEESA-2) : A randomized double-blind, placebo-controlled Phase III study of ribociclib in combination with letrozole for the treatment of postmenopausal women with HR+, HER2-negative advanced breast cancer who received no prior therapy for advanced disease.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to make some editorial changes in the SmPC and the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Lithuania and Estonia.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

This application does not include significant changes to the currently approved Kisqali PL and therefore the results of the initial consultation with the target patient population are still considered valid and it is not considered necessary to perform any new user testing for this variation application.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kisqali (ribociclib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed change of indication is:

"Kisqali is indicated for the treatment of ~~postmenopausal~~ women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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 luteinizing hormone releasing hormone (LHRH) agonist."

3.1.2. Available therapies and unmet medical need

Breast cancer is estimated to cause about 500 000 deaths worldwide annually. A proportion of patients will eventually relapse with progression of the disease. For ER+, HER2-negative patients, the following treatment options are relevant as initial endocrine-based therapy or in women who have received prior endocrine therapy:

- First line endocrine therapy; aromatase inhibitors (AI), tamoxifen, fulvestrant, AI + CDK4/6 inhibitor, AI + everolimus (conditional on adjuvant AI).
- Second line endocrine therapy; AI, tamoxifen, fulvestrant, fulvestrant + palbociclib, AI + everolimus, and megestrol acetate.

According to treatment guidelines, chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance.

3.1.3. Main clinical studies

Two trials support the change of indication:

- Study CLEE011E2301 (MONALEESA 7)

  A randomised, double blind, placebo controlled, multicentre phase III clinical study in the treatment of pre- and perimenopausal women with hormone receptor positive, HER2 negative advanced breast cancer in combination with a NSAI or tamoxifen plus goserelin versus placebo in combination with a NSAI or tamoxifen plus goserelin.

  Due to safety concerns regarding QT prolongation for the combination with tamoxifen, the applicant proposes not to include the use of ribociclib in combination with tamoxifen.

- Study CLEE011F2301 (MONALEESA 3)

  A randomised double blind, placebo controlled, multicentre phase III clinical study in the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative advanced breast cancer who had received no or only one line of prior endocrine treatment, in combination with fulvestrant versus fulvestrant alone.

3.2. Favourable effects

MONALEESA 7 (E2301):

- PFS by investigator (primary endpoint), median 23.8 vs. 13.0 months in ribociclib + NSAI/tamoxifen vs. placebo + NSAI/tamoxifen, HR 0.55 ($p = 9.8 \times 10^{-8}$). Event rate 39% vs. 56%.
- OS, median NR vs. 29.4 months, HR 0.92 (p= 0.34). Event rate 13% vs. 14%.

MONALEESA 3 (F2301):

- PFS by investigator (primary endpoint), median 20.5 vs. 12.8 months in ribociclib + fulvestrant vs. placebo + fulvestrant, HR 0.59 ($p = 4.1 \times 10^{-7}$). Event rate 43% vs. 62%.
- OS, median NR vs. NR, HR 0.67 (p= 0.015). Event rate 15% vs. 21%.

3.3. Uncertainties and limitations about favourable effects

Overall survival data is immature with <15% event rate in MONALEESA 7 and 3. Thus, the post progression disease-course is uncertain. Nevertheless, a detrimental OS effect is unlikely given the large treatment-effect on PFS and based on the evaluation of deaths on study and in follow up. The results of the next OS interim analysis and the final analysis are expected to be provided for the two clinical studies post-authorisation as soon as available.

3.4. Unfavourable effects

Whereas study A2301 (MONALEESA 2) studied ribociclib in combination with an AI in a population of postmenopausal women, the E2301 study (MONALEESA 7) investigated the combination in pre-/ peri-menopausal women (with the addition of goserelin). No differences were observed in the overall safety profile and individual AEs reported in study E2301 as compared to study A2301 other than an overall higher proportion of AEs by severity and SAEs reported in study A2301. This may in part reflect the age differences in the respective patient populations studied (median 43 and 62 years of age in E2301 and A2301 respectively).

The application for approval for the indication in combination with fulvestrant is mainly based on the F2301 study (MONALEESA 3) enrolling postmenopausal women to receive ribociclib + fulvestrant (N=483) vs. placebo + fulvestrant (N=241) as 1st or 2nd line (after only one line of prior endocrine treatment). Also male

breast cancer patients were eligible but none were enrolled. The safety profiles between ribociclib + AI and ribociclib + fulvestrant are considered similar.

Overall, the most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥2%, respectively) in the pooled dataset for which the frequency for Kisqali plus letrozole any combination exceeds the frequency for placebo plus letrozole any combination were infections, neutropenia, leukopenia, headache, cough, back pain, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash, and infections, neutropenia, leukopenia, anaemia, abnormal liver function tests, lymphopenia, hypophosphataemia, and vomiting, nausea, fatigue and back pain, respectively.

The available data are sufficient for a reasonable characterization of the safety profile in the long term perspective.

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the rats or rabbits. Furthermore, ribociclib and its metabolites passed readily into rat milk. Considering available non clinical data, the SmPC has been adequately updated to include warnings and precautions in relation to pregnancy and breastfeeding.

The SmPC has also been adequately updated to revise the frequencies of adverse drug reactions based on the pooled dataset (A2301, E2301 and F2301) and add the following new ADRs: infections, cough, dry skin, vertigo, oropharyngeal pain, rash pruritic, abdominal pain upper, vitiligo, dizziness and dry mouth. Apart from these changes, there are no new safety concerns or signals identified in either the E2301 or the F2301 study.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties about unfavourable effects.

3.6. Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Study CLEE011E2301 (MONALEESA-7) - **Kisqali in combination with NSAI or tamoxifen, 1st endocrine line in the advanced setting for HR positive, HER2-negative breast cancer.**					
Favourable effects (full analysis set)					
PFS	Progression-free survival (95% CI)	Months	23.8 (19.2 – NE)	13.0 (11.0 – 16.4)	HR 0.55 (0.44 – 0.69) P-value: 9.8 x 10^{-8} Event rate 39% vs. 56% Supported in independent review of 40% of patients (BIRC)
OS	Overall survival (95% CI)	Months	NE (NE – NE)	29.4 (28.2 – NE)	HR 0.92 (0.60 – 1.4) P-value: 0.34 Event rate 13% vs. 14%
Favourable effects in 495 patients with NSAI as endocrine combination partner					
PFS	Progression-free survival (95% CI)	Months	27.5 (19 – NE)	13.8 (13 – 17)	HR 0.57 (0.44 – 0.74) Event rate 37% vs. 53%
OS	Overall survival	Months	NE	29.4	HR 0.80 (0.49 – 1.30)

	(95% CI)		(NE – NE)	(28.2 – NE)	Event rate 12% vs. 15%
Study CLEE011F2301 (MONALEESA-3) - **Kisqali in combination with fulvestrant, 1st and 2nd endocrine line in the advanced setting for HR positive, HER2-negative breast cancer.**					
Favourable effects					
PFS	Progression-free survival (95% CI)	Months	20.5 (18.4 – 23.5)	12.8 (10.9 – 16.3)	HR 0.59 (0.48 – 0.73) P-value: 4.1 x 10^{-7} Event rate 43% vs. 62% Supported in independent review of 40% of patients (BIRC)
OS	Overall survival (95% CI)	Months	NE (NE – NE)	NE (NE – NE)	HR 0.67 (0.47 – 0.96) P-value: 0.015 Event rate 15% vs. 21%

Unfavourable Effects

F2301 (MONALEESA-3)		**Ribociclib + fulvestrant N=484**	**Placebo + fulvestrant N=242**	Median duration of exposure to study treatment was 16 months for the R+F arm vs. 12 months in the control arm.	
Drug related AEs - Any - Grade 3 - Grade 4	% 95.4 56.7 10.8	 68.0 6.6 1.2			
AE leading to dose reduction of ribociclib or placebo	%	33.1	3.3		
AE leading to dose interrupt of ribociclib or placebo	%	68.5	18.7		
AE leading to discontinuation	%	8.5	4.1		
Neutropenia - Any - Grade 3 - Grade 4	% 55.9 36.6 5.8	 0.8 0 0			
Nausea - Any - Grade 3 - Grade 4	% 45.3 1.4 0	 28.2 0.8 0			
Fatigue - Any - Grade 3 - Grade 4	% 31.5 1.7 0	 33.2 0.4 0			
Diarrhoea - Any - Grade 3 - Grade 4	% 29.0 0.6 0	 20.3 0.8 0			
Vomiting - Any - Grade 3 - Grade 4	% 26.7 1.4 0	 12.9 0 0			

ALT/ AST increased - Any - Grade 3 - Grade 4	%	 14.5/ 13.3 6.6/ 4.8 1.9/ 1.2	 4.6/ 4.6 0.4/ 0.8 0/ 0		
QT prolongation - Any - Grade 3 - Grade 4	%	 6.2 1.4 0	 0.8 0.4 0		
E2301 (MONALEESA-7)		**Ribociclib + AI + goserelin N=248**	**Placebo + AI + goserelin N=247**	Median duration of exposure to study treatment was 15 months for the R+AI+G arm vs. 12 months in the control arm.	
Drug related AEs - Any - Grade 3/ Grade 4	%	 92.7 69.4	 70.0 10.1		
AEs leading to ≥ 1 dose reduction	%	33.3	6.1		
AE leading to ≥ 1 dose interrupt of ribo or placebo	%	69.9	15.5		
AEs leading to discontinuation	%	6.5	3.2		
Neutropenia - Any - Grade 3 - Grade 4	%	 56.5 39.1 6.0	 4.9 1.6 0		
Nausea - Any - Grade 3 - Grade 4	%	 31.5 0 0	 20.2 0 0		
Fatigue - Any - Grade 3 - Grade 4	%	 23.4 0.8 0	 25.1 0 0		
Diarrhoea - Any - Grade 3 - Grade 4	%	 19.8 2.0 0	 18.6 0 0		
Vomiting - Any - Grade 3 - Grade 4	%	 17.3 0.8 0	 17.0 0 0		
ALT/ AST increased - Any - Grade 3 - Grade 4	%	 13.3/ 12.9 4.8/ 3.6 0/ 0	 8.9/ 10.1 1.2/ 1.2 0/ 0		
QT prolongation - Any - Grade 3 - Grade 4	%	 9.3 1.2 0	 3.2 0 0		

Abbreviations: ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, DILI- Drug-induced liver injury

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In advanced breast cancer, a PFS gain of 11 months in first line use of ribociclib as add on to a non-steroidal AI compared to NSAI alone in premenopausal patients, and a PFS gain of 8 months for the 1st and 2nd line population assessed in the fulvestrant add-on study, is considered clinically relevant and important. The effect sizes observed are consistent with other approved CDK4/6 inhibitors.

The safety from study E2301 investigating ribociclib in combination with an AI in a population of pre/perimenopausal women is similar to the safety data from study A2301 performed in postmenopausal women. Therefore, no new concerns have been raised during the study which reflects the known safety profile of ribociclib. The safety profile is also in line with the safety of ribociclib in combination with fulvestrant suggesting that no differences in the safety profile are expected depending on the choice of accompanying endocrine therapy. No new signals or concerns were raised from the safety database from the two studies. The important safety concerns with ribociclib are myelosuppression (primarily neutropenia), hepatobiliary toxicity and QT interval prolongation which are considered to be adequately reflected in the SmPC as well as covered in the RMP.

3.7.2. Balance of benefits and risks

Study MONALEESA 7 (study E2301) showed a clinical relevant effect in PFS for the combination therapy of ribociclib with an aromatase inhibitor and an LHRH agonist as initial endocrine therapy in pre/peri-menopausal women with HR positive, HER2 negative advanced breast cancer. Study MONALEESA 3 (study F2301) also showed a clinical relevant effect in PFS for the combination with fulvestrant as initial endocrine-based therapy, or after progression on one line of endocrine therapy in postmenopausal women with HR positive, HER2 negative advanced breast cancer. Although the OS data from the two studies are still immature, a detrimental effect is unlikely given the large treatment-effect on PFS and based on the evaluation of deaths.

The toxicity of ribociclib regardless of accompanying endocrine therapy is considered manageable with appropriate risk minimization measures as described in the product information and in the RMP.

The extrapolation to ribociclib in combination with fulvestrant + LHRH in pre/perimenopausal women is accepted. Efficacy has been shown for ribociclib in combination with fulvestrant in postmenopausal women (MONALEESA 3 (study F2301)), and in combination with aromatase inhibitors in premenopausal women (MONALEESA 7 (study E2301)), supporting the extrapolation. Fulvestrant is an accepted option for premenopausal patients as effective inhibition of ER signalling is achieved with fulvestrant or AI alike (+LHRH).

The extrapolation of the indication for second-line use of ribociclib in combination with AI can be supported by the demonstrated add-on effect to fulvestrant in the second line (Study F2301) as well as the evidence of the efficacy demonstrated in first line in combination with AI (Study E2301).

Based on the above, the benefit/risk balance of ribociclib for the 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 is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of ribociclib for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (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 is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant for Kisqali; in pre- or perimenopausal women, the endocrine therapy (aromatase inhibitor or fulvestrant) should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist. The extension to the indication is based upon data from study CLEE011E2301 (A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer) and study CLEE011F2301 (A randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2 negative, advanced breast cancer who have received no or only one line of prior endocrine treatment).
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1 and 5.3 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and to make an administrative update to the Estonian and Latvian local representatives addresses in the Package Leaflet. An updated RMP version 3.0 was agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).