17 October 2024
EMA/CHMP/512303/2024
Committee for Medicinal Products for Human Use (CHMP) Corr.1[1]

Assessment report

Kisqali

International non-proprietary name: Ribociclib

Procedure No. EMEA/H/C/004213/II/0045

Note

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

[1] 3 February 2025 to correct a statement in section 3.3 'Uncertainties and limitations about favourable effects'

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List of abbreviations

aBC	Advanced breast cancer
ADR	Adverse drug reaction
AE	Adverse event
AI	Aromatase inhibitor
ANC	Absolute neutrophil count
AUC	Area under the concentration-time curve
BC	Breast cancer
CDK4/6	Cyclin-dependent kinase 4/6
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off date
DDFS	Distant disease-free survival
DFS	Disease-free survival
DMC	Data Monitoring Committee
DRFS	Distant recurrence-free survival
eBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
eCRS	Electronic Case Retrieval Strategy
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ET	Endocrine therapy
ET only arm/group	Letrozole or anastrozole, plus goserelin (if applicable)
FAS	Full Analysis Set
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scales
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
iDFS	Invasive disease-free survival
ILD	Interstitial lung disease
IRT	Interactive response technology
LRRFS	Loco-regional recurrence-free survival
MedDRA	Medical Dictionary for Regulatory Activities
NSAI	Nonsteroidal aromatase inhibitor
OS	Overall survival
PAES	Post Approval Efficacy Study
PARP	Poly (ADP-ribose) polymerase
PD	Pharmacodynamics
PFS	Progression-free survival
PgR	Progesterone receptor
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PPS	Per-protocol set
PRO	Patient-reported outcome
PSUR	Periodic Safety Update Report

RFS	Recurrence-free survival
RMM	Repeated measures model
SAE	Serious adverse event
SC	Steering Committee
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SEER	Surveillance, Epidemiology, and End Results
STEEP	Standardized Definitions for Efficacy End Points (in Adjuvant Breast Cancer Trials)
TTR	Time to response
VAS	Visual analog scale

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 25 August 2023 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 the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, Stage II or Stage III early breast cancer, irrespective of nodal status, in combination with an AI for Kisqali based on study CLEE011O12301C (NATALEE); This is a global, Phase III, multicentre, randomized, open-label trial to evaluate efficacy and safety of ribociclib with ET versus ET alone as adjuvant treatment in patients with HR-positive, HER2-negative, early breast cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation requested 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) on the granting of a (product-specific) 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 MAH 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 MAH sought advice at the CHMP on 23 Nov 2016 and 01 Nov 2018.

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	25 August 2023
Start of procedure:	16 September 2023
CHMP Rapporteur Assessment Report	10 November 2023
PRAC Rapporteur Assessment Report	16 November 2023
CHMP Co-Rapporteur Assessment	22 November 2023
PRAC members comments	22 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	04 December 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2023
Request for supplementary information (RSI)	14 December 2023
MAH's responses submitted to the CHMP on:	18 January 2024
CHMP Rapporteur Assessment Report	20 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC members comments	28 February 2024
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	07 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
MAH's responses submitted to the CHMP on:	23 May 2024
Rapporteur's assessment report on the MAH's responses circulated on:	01 July 2024
CHMP members comments	15 July 2024
Rapporteur's updated assessment report circulated on:	18 July 2024
Request for supplementary information (RSI)	25 July 2024
MAH's responses submitted to the CHMP on:	13 August 2024
Rapporteur's assessment report on the MAH's responses circulated on:	23 September 2024
CHMP members comments	07 October 2024
Rapporteur's updated assessment report circulated on:	10 October 2024
CHMP opinion:	17 October 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed indication is:

> *Kisqali is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer, irrespective of nodal status, in combination with an aromatase inhibitor.*

The final indication has been amended as follows:

> *Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria).*

In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Epidemiology

Breast cancer (BC) is the most frequently diagnosed cancer among women worldwide. Approximately 2.3 million new cases of BC and 685,000 deaths attributed to this disease were estimated to occur in 2020 worldwide. BC incidence varies between individuals of different ethnicities and in different geographic locations around the world. In Europe, the estimated incidence of BC in 2020 was approximately 531,000, with 142,000 deaths (GLOBOCAN 2020). Breast cancer in men is uncommon, with a reported frequency of approximately 1% of all BC (Eggemann et al 2013).

Biologic features

BC is a molecularly diverse disease with several clearly defined molecular subgroups (Perou et al 2000). Clinically, the three therapeutic subgroups are HR-positive breast cancer (oestrogen and/or progesterone receptor-positive with normal HER2 expression), HER2-positive breast cancer characterized by HER2 gene amplification or overexpression (approximately 45% of these cancers are HR-positive), and triple-negative breast cancer characterized by low or absent hormone receptors and absence of HER2 alteration.

Approximately 60-65% of new BC cases are HR-positive and benefit from adjuvant endocrine therapy (ET), which reduces the risk of recurrence and, ultimately, cancer death. Resistance to ET, however, continues to be a clinical problem.

The cyclin-dependent kinase (CDK) 4/6 complex is involved in DNA synthesis and cell cycle progression via interaction with cyclin D1 and the retinoblastoma protein (pRb). Oestrogen receptor (ER)-positive BC seems to be particularly dependent on the CDK4/cyclin D1/Rb interaction, which, concurrently, is often dysregulated in BC. CDK4/6/cyclin D1/Rb interaction thus constitutes a potential target for targeted therapies in HR-positive BC.

Clinical presentation, diagnosis

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

Management

The treatment goal for patients with eBC is prevention of both early and late recurrences and, subsequently, death due to BC.

Treatment of patients with HR-positive, HER2-negative eBC consists of surgery and combinations of adjuvant ET, radiotherapy, and neoadjuvant and/or adjuvant chemotherapy. The systemic treatments are typically considered for patients at risk for recurrence, including stage II and III disease with larger tumour size and/or metastases in multiple regional lymph nodes, high tumour grade, and high recurrence genomic score, or a combination of these. Adjuvant systemic treatments in patients with eBC have been shown to decrease locoregional and distant recurrences, reduce the risk of recurrence and BC deaths, and to improve 15-year breast cancer mortality (Clarke et al 2005). According to current ESMO and NCCN clinical guidelines, pre- and postmenopausal women with HR-positive eBC are recommended adjuvant ET. For premenopausal women and for men, standard adjuvant ET consists of tamoxifen or an aromatase inhibitor (AI) + a luteinizing hormone-releasing hormone (LHRH). For postmenopausal women, adjuvant ET consists of either an AI (letrozole, anastrozole, or exemestane) or tamoxifen, alone or sequential treatment.

Despite adjuvant ET, recurrences are still common. Approximately 30-60% of patients with stage II and III BC suffer from recurrent disease. The risk of recurrence in patients with HR-positive, HER-2 negative eBC is highest during the first 5 years after diagnosis, but still more than half of those who recur experience late recurrences (≥ 5 years from diagnosis). In women with ER-positive eBC who were disease-free after 5 years of adjuvant ET, the cumulative 20-year risk of distant recurrence is approximately 22% for patients without lymph node metastases and 31-52% for those with nodal disease. The corresponding cumulative 20-year risks of death from BC based on nodal status (N0, N1-3, N4-9) are 15%, 28%, and 49%, respectively (Pan et al 2017). Currently, abemaciclib in combination with ET is the only CDK4/6 inhibitor indicated for adjuvant treatment of HR-positive, HER2-negative eBC with high risk of recurrence (see Verzenios EPAR).

2.1.2. About the product

Ribociclib is an oral, selective small molecule inhibitor of the CDK4/6 enzyme complex, which targets the pRb to block cell cycle progression. The inhibition of CDK4/6 can delay or overcome endocrine resistance and thereby enhance the effectiveness of ET.

The current submitted indication is in Early breast cancer

The recommended dose is 400 mg (two 200 mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. In patients with early breast cancer, Kisqali should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur.

Previously the product was approved for Advanced or metastatic breast cancer

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. In patients with advanced or metastatic breast cancer, the treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Ribociclib as well as the CDK4/6 inhibitors abemaciclib and palbociclib are indicated for treatment of advanced or metastatic BC in combination with ET (see Kisqali EPAR).

Ribociclib has been studied in combination with various hormonal and other agents in cancer patients.

- Ribociclib + letrozole vs. letrozole monotherapy was investigated in the phase III study MONALEESA-2 in postmenopausal women with HR-positive, HER2-negative, advanced BC (aBC) without prior therapy for advanced disease.
- Ribociclib in combination with either a non-steroidal AI (NSAI) or tamoxifen and goserelin vs. placebo in combination with either an NSAI or tamoxifen and goserelin was investigated in the phase III study MONALEESA-7 in pre- and perimenopausal women with HR-positive, HER2-negative aBC without prior ET for advanced disease.
- Ribociclib + fulvestrant vs. fulvestrant monotherapy was investigated in the phase III study MONALEESA-3 in postmenopausal women with HR-positive, HER2-negative aBC who had received no or only one line of prior ET.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Development programme

The primary claim for treatment of HR-positive, HER2-negative eBC with ribociclib + AI is based on the pivotal study CLEE011O12301C (`study O12301C´). Ribociclib is not indicated in combination with tamoxifen, and in study O12301C all patients were treated with the AIs letrozole or anastrozole. Premenopausal women plus men also received the gonadotropin-releasing hormone (GnRH) agonist goserelin for gonadal suppression.

Scientific advice

On 23 Nov 2016 the Applicant Novartis requested scientific advice for their product ribociclib. At that time, Novartis sought advice from the CHMP and SAWP concerning the pre-clinical and clinical development of their intended phase III study in eBC patients with high risk of recurrence.

In summary, the CHMP agreed on the Applicant's approach to assess the carcinogenic potential of ribociclib using a stepwise procedure in a 2-year rat carcinogenicity study. The outcome of the rat carcinogenicity study was requested to be included in the application for extension of indication for adjuvant treatment. It was noted that, eventually, a study in a transgenic mouse model should be considered before MAA.

Furthermore, the Applicant proposed two clinical studies, one in eBC patients with high risk of recurrence and one in eBC patients with intermediate risk of recurrence. For both the CHMP overall agreed on the target population and study design. The endpoints were endorsed with some recommendations. Furthermore, the Applicant was advised to plan adequate collection of OS data.

The proposed dosage (600 mg daily orally in a 3 weeks on/1 week off schedule) was endorsed but a justification of the proposed treatment duration was requested and different treatment durations (e.g., one and two years) in the phase 3 study was advised.

On 01 Nov 2018 Novartis requested scientific advice for their product ribociclib (EMA/CHMP/SAWP/113188/2019) as follow-up to the previous advice where two different studies were suggested, one in stage II and one in stage III. The Applicant proposed to evaluate both study populations in one pivotal study. No detailed reasons were given, but the Applicant stated that the change was not due to safety reasons.

Because of the changed study design, the overall sample size was proposed to be reduced. It was noted by the CHMP that study heterogeneity may be further increased when different target populations are combined. The approach evaluating an overall population within one pivotal study was not rejected but the Applicant was requested to ensure sufficiently high recruitment numbers to allow the demonstration of internal consistency of efficacy and safety across the relevant subpopulations in this heterogeneous overall population. As a consequence of the CHMP critique, the MAH amended the overall sample size of the study from 4,000 to 5,000 in protocol amendment 4.0, 27-Aug-2020 (addition of 1,000 patients with stage III disease).

Furthermore, the Applicant proposed to cap enrolment of stage II and III patients at 40% and 60%, respectively. The CHMP highlighted that from a clinical perspective this study population would not be representative for the population being treated in clinical practice out of trials. The weighting of stage II and stage III in the statistical analysis will depend on the proportion of events that are contributed by each stratum such that it is counterintuitive to even increase the proportion of stage III patients with a higher event risk compared to the natural distribution. The Applicant expected a consistent treatment effect in terms of hazard ratio for stage II and stage III patients and justified the capping by an expected shorter study duration. The assessment of the consistency assumption will be of paramount importance to justify that the results as observed in the study population can be generalised to the overall patient population.

The Applicant furthermore proposed a lower ribociclib dosage (400 mg) and longer treatment duration (36 months) than previously discussed. It was considered that the dose reduction may not be well underpinned and that the treatment duration needed further justification, not least taking into account that the long-term safety of ribociclib was undetermined.

The endpoints were endorsed but the Applicant was recommended to continue collecting iDFS data to provide analyses in line with EMA censoring rules. Furthermore, the Applicant was advised to plan adequate collection of OS data.

On 29 June 2023 a pre-submission with the Applicant and the Rapporteurs was held. The Rapporteurs noted that given the adjuvant setting of the indication and the high percentage of patients still on treatment at the time of the presented data lock-point, a longer follow up period will be required to sufficiently assess the benefit/risk. The applicant anticipated a data update at 500 events, probably available at the time of responses to the first round of questions. The MAH was informed that these data will be required for decision-making.

Furthermore, the MAH has received scientific advice from the FDA regarding the endpoint overall survival (OS) and regarding treatment duration. The FDA asked if the study O12301C SAP would include formal testing for OS but given the stage II and stage III eBC patient population the event rate for OS was expected to be low, and so it was considered impractical to statistically power an analysis of OS. OS was, however, added as a secondary endpoint.

The optimal duration of ribociclib treatment in the adjuvant setting was discussed but ultimately left for the Sponsor decision. Data supported a higher risk of disease recurrence during the first three years after surgical resection. According to the Applicant, an extended duration of treatment is critical to prolong cell cycle arrest and drive more tumour cells into senescence/death and, thus, a 3-year duration of treatment was chosen for the study.

The following recommendation is not considered completely met in the application:

- Study O12301C is an open-label study. Radiologic review is assessed locally, and not centrally reviewed. As was stated in the scientific advice on 23 Nov 2016, this was not agreed upon. All efforts must be made to keep the strictest parallelism in the assessments between arms to minimise the risk of bias when the study is not double-blinded.

2.1.4. General comments on compliance with GCP

The MAH states that the study is conducted in compliance with GCP. The MAH 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.

2.2. Non-clinical aspects

2.2.1. Introduction

Kisqali contains a nitrosamine impurity (N-NRib) which levels, have been so far regulated by ICH Q3B in accordance with ICH S9 for the currently approved indication of locally advanced and metastatic breast cancer.

The current extension of indication application aims to treat early breast cancer in an adjuvant setting hence the exception in ICH S9 is not applicable and would need to follow ICH M7 guidance for non-clinical development.

2.2.2. Toxicology

Genotoxicity

The N-nitrosoribociclib impurity (N-NRib) is present in trace amounts in ribociclib succinate drug substance and in Ribociclib 200 mg film-coated tablet. N-NRib was tested in three separate Ames tests, all concluding that N-NRib did not induce mutations under the test conditions. However, N-NRib was determined to be mutagenic in an in vivo transgenic rodent (TGR) gene mutation assay (Muta™Mouse study). N-NRib limits need to be controlled using the carcinogenic potency categorization approach (CPCA) by applying a maximum acceptable intake (AI) of 400 ng/day (category 3).

The applicant proposed changes to the quality module to include measures to minimize the formation of the N-NRib impurity and to ensure control of N-NRib in compliance with the acceptable intake of 400 ng/day for early breast cancer and considering a Maximum Daily Dose (MDD) of 400 mg for the proposed early breast cancer indication which are assessed in procedure EMEA/H/C/004213/II/0054/G.

N-NRib was tested in three separate Ames tests: one enhanced Ames test (EAT) applying EAT conditions and two supportive tests, one standard Ames test (not an EAT) and one externally conducted Ames (partly EAT conditions).

Table 1. Tabular summary of in vitro and in vivo mutagenicity assays performed for N-NRib

Novartis Ref. 2371003	N-NRib: Transgenic Gene Mutation Assay in Muta™Mice (the objective of this study is to evaluate the induction of gene mutation in the lacZ transgene in bone marrow, liver, kidney and duodenum from Muta™Mice (CD2-lacZ80/HazfBR strain)).
Novartis Ref. 2370992	Bacterial Reverse Mutation Assay using the Enhanced Ames protocol (the objective of this study is to evaluate the ability of N-NRib to induce reverse mutations in histidine-requiring strains of Salmonella typhimurium and one tryptophan-requiring strain of Escherichia coli in the absence and presence of a 30% rat and 30% hamster liver metabolising system (S-9))
Novartis Ref. 2112503	Bacterial Reverse Mutation Assay (The objective of the Salmonella/microsome assay is to evaluate the mutagenic potential of a test item by its effects on one or more histidine-requiring strains of Salmonella typhimurium in the absence and presence of a 10% rat liver metabolising system) non-regulatory study for which a claim of GLP compliance was not made. However, the laboratory procedures were conducted in accordance with the current GLP requirements of the UK MHRA and OECD.

Table 2. Summary of Bacterial Reverse Mutation Assay in vitro using the Enhanced Ames Test protocol (23709992)

Genotoxicity: in vitro (23709992): Bacterial Reverse Mutation Assay	
Test for induction of	Reverse Mutations (Enhanced Ames Test)
Strains	*Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 *uvrA* pKM101
Metabolizing System	β-Naphthoflavone/Phenobarbital induced rat or hamster liver S-9 (30%)
Vehicles: For Test item: For Positive Controls:	 Dimethyl formamide (DMF) Dimethyl Sulphoxide (DMSO) (2NF, AAC, AAN, B[a]P, NQO, NDEA, MNPA), Purified water (NAN3)
No. of Independent Assays:	1
No. of Replicates:	3
No. Cells/Analysed/Culture:	10^8/plate
Treatment:	Pre-incubation (30 minutes)
Date of Treatment:	12 December 2023
Novartis Reference No:	2370992
GLP Compliance:	Yes
Toxic Effects:	Evidence of toxicity in the form of a reduction in revertant numbers was observed at 750 µg/plate and above in strain TA100 in the presence of

Genotoxicity: in vitro (23709992): Bacterial Reverse Mutation Assay	
	hamster S-9 and at 1000 µg/plate in strain TA1537 in the presence of hamster S-9
Genotoxic Effects:	None

Table 3. Raw plate counts without activation

			Mutation Experiment				
Metabolic Activation	**Test Item**	**Concentration (µg/plate)**	**Revertants/Plate (Mean)**				
			TA98	**TA100**	**TA1535**	**TA1537**	**WP2 *uvrA* pKM101**
	DMF	0	17	115	20	8	190
Without	DMP433	5	18	118	11	8	182
Activation	DMP433	16	15	108	9	8	149
	DMP433	50	15	117	13	11	164
	DMP433	160	14	128	12	7	145
	DMP433	500	17	134	12	9	160
	DMP433	750	18 P	107 P	12 P	10 P	142 P
	DMP433	1000	18 P	113 P	14 P	10 P	167 P
	Positive Control	Compound	2NF	NaN_3	NaN_3	AAC	NQO
		Concentration (µg/plate)	5	2	2	50	2
		Revertants	1832	1070	891	277	1726

Table 4. Raw plate counts without activation

			Mutation Experiment				
Metabolic Activation	**Test Item**	**Concentration (µg/plate)**	**Revertants/Plate (Mean)**				
			TA98	**TA100**	**TA1535**	**TA1537**	**WP2 *uvrA* pKM101**
	DMF	0	36	156	19	25	203
With	DMP433	5	39	143	21	18	212
Activation	DMP433	16	33	137	19	20	229
30% Rat	DMP433	50	39	123	16	18	211
S-9	DMP433	160	40	122	18	27	201
	DMP433	500	31	121	24	20	220
	DMP433	750	38 P	121 P	17 P	23 P	201 P
	DMP433	1000	39 P	117 P	19 P	25 P	186 P
	DMSO	0	62	184	26 M	18 C M	192
	NDEA	1250	54	235	23	20	518
	NDEA	2500	59	270	31	32	702
	NDEA	5000	65	311	26	15	928
	MNPA	500	51 C M	1041	558	16	903
	MNPA	1600	61	1116	413	22	875
	Positive Control	Compound	B[a]P	AAN	AAN	AAN	AAN
		Concentration (µg/plate)	10	5	5	5	10
		Revertants	269	1568	184	31	643

Metabolic Activation	Test Item	Concentration (µg/plate)	Mutation Experiment Revertants/Plate (Mean)				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
With Activation 30% Rat S-9 (continued)	Positive Control	Compound	-	-	-	AAN	-
		Concentration (µg/plate)	-	-	-	8	-
		Revertants	-	-	-	42	-
	Positive Control	Compound	-	-	-	AAN	-
		Concentration (µg/plate)	-	-	-	1.25	-
		Revertants	-	-	-	32 M	-
	Positive Control	Compound	-	-	-	B[a]P	-
		Concentration (µg/plate)	-	-	-	7.5	-
		Revertants	-	-	-	85 M	-
	Positive Control	Compound	-	-	-	B[a]P	-
		Concentration (µg/plate)	-	-	-	10	-
		Revertants	-	-	-	88	-

Metabolic Activation	Test Item	Concentration (µg/plate)	Mutation Experiment Revertants/Plate (Mean)				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
	DMF	0	47	180 C M	30	23	228
With Activation 30% Hamster S-9	DMP433	5	36	117 W C M	31	22	304
	DMP433	16	39	103 W M	25 W M	19	225
	DMP433	50	41	115 W M	23 W M	20	221
	DMP433	160	40	102 W M	18 W M	16	242
	DMP433	500	40	107 W M	17 W M	22	214
	DMP433	750	36 P	98 W P M	17 W P M	16 P	172 P
	DMP433	1000	41 P	97 W P M	21 W P M	12 P	194 P
	DMSO	0	38 M	145	26	19	188
	NDEA	1250	87	570	103	24	966
	NDEA	2500	116	1048	109	20	1306
	NDEA	5000	157	1449	177	28	1392
	MNPA	500	89	1535	1304	21	736
	MNPA	1600	116	1460	1361	25	805
	Positive Control	Compound	B[a]P	AAN	AAN	AAN	AAN
		Concentration (µg/plate)	10	5	5	5	10
		Revertants	657	2862	392	38	804

Metabolic Activation	Test Item	Concentration (µg/plate)	Mutation Experiment Revertants/Plate (Mean)				
			TA98	TA100	TA1535	TA1537	WP2 *uvrA* pKM101
With Activation 30% Hamster S-9 (continued)	Positive Control	Compound	-	-	-	AAN	-
		Concentration (µg/plate)	-	-	-	8	-
		Revertants	-	-	-	121	-
	Positive Control	Compound	-	-	-	AAN	-
		Concentration (µg/plate)	-	-	-	1.25	-
		Revertants	-	-	-	35	-
	Positive Control	Compound	-	-	-	B[a]P	-
		Concentration (µg/plate)	-	-	-	7.5	-
		Revertants	-	-	-	139	-
	Positive Control	Compound	-	-	-	B[a]P	-
		Concentration (µg/plate)	-	-	-	10	-
		Revertants	-	-	-	155	-

Footnotes to tables:

Key to postfixes:

P: Precipitation of test item observed

M: Plate counted manually

C: Contaminated plate

W: Wet plate

2NF 2-Nitrofluorene

NaN_3 Sodium azide

AAC 9-Aminoacridine

NQO 4-Nitroquinoline-1-oxide

B[a]P Benzo[a]pyrene

AAN 2-Aminoanthracene

Means values are generated from unrounded values exported directly from data capture software, and so may appear to vary from those presented to 1 decimal place in the study report.

In vivo Muta™Mouse study with the the nitrosamine impurity N-NRib

N-NRib induced dose dependent mutations in the lacZ transgene at all doses tested (25, 50 or 100/80 mg/kg/day) in liver and duodenum of male mice. An increase in mutant frequency (MF) was also noted in duodenum in female high dose mice (below tables). No biological relevant increases of mutant frequencies were noted in bone marrow and kidneys of either sex.

Table 5. Mutant frequency in liver from male mice male mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
1	Vehicle control	0	45.17	15.407	-
2	DMP433	25	81.05	27.843	0.0286 (P≤0.05)
3	DMP433	50	117.71	51.243	0.0010 (P≤0.001)
4	DMP433	100/80†	180.30	116.303	0.0005 (P≤0.001)
N/A	Positive Control	50	278.18	36.408	<0.0001 (P≤0.001)

Dose response (Group 1, 2, 3, 4): P = <0.0001 (P≤0.001)
† Dose level reduced to 80 mg/kg/day as of Day 4 of dosing due to mortality/morbidity.

Table 6 Mutant frequency in duodenum from male mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
1	Vehicle control	0	46.02	8.825	-
2	DMP433	25	115.91	22.140	0.0002 (P≤0.001)
3	DMP433	50	127.28	44.300	<0.0001 (P≤0.001)
4	DMP433	100/80†	203.88	53.694	<0.0001 (P≤0.001)
N/A	Positive Control	50	1058.93	139.852	<0.0001 (P≤0.001)

Dose response (Group 1, 2, 3, 4): P = <0.0001 (P≤0.001)
† Dose level reduced to 80 mg/kg/day as of Day 4 of dosing due to mortality/morbidity.

Table 7. Mutant frequency in duodenum from female mice

Group	Treatment	Dose (mg/kg/day)	Group Mean MF (x 10^{-6})	SD	P-value
5	Vehicle control	0	40.21	9.569	-
6	DMP433	100	236.21	74.466	<0.0001 (P≤0.001)
N/A	Positive Control	50	1035.50	88.774	0.0028 (P≤0.01)

2.2.3. Ecotoxicity/environmental risk assessment

Ribociclib is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that induces G1 arrest at sub-micromolar concentrations in a variety of pRb-positive cancer cells in vitro.

The ERA initially submitted in the context of the initial MAA has been updated by means of newly calculated Predicted Exposure Concentrations (PECs), which are based on prevalence data for the target indication.

Table 8. Summary of main study results

Substance (INN): ribociclib			
CAS-number (if available): 1211441-98-3 (free base); 1374639-75-4 (succinate salt)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD107	log D at pH 4 < -0.8 log D at pH 7 = 0.6 log D at pH 9 = 2.2	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow} (highest in pH range 4 to 9)	2.2	not B
	BCF	N/A	-
Persistence	DT50 (OECD 308; recalculated to 12°C)	0.66 to 0.74 days	not P
Toxicity	NOEC		T
PBT-statement :	The compound is considered as not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater refined (e.g. prevalence, literature)	0.147	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = Loamy sand Soil 2 = Sandy loam Soil 3 = Clay Sludge 1 = Tilburg Sludge 2 = Aa & Maas	OECD 106	*K*oc Soil1 = 41886 L/kgoc K_{oc} Soil2 = 69250 L/kg_{oc} K_{oc} Soil3 = 301755 L/kg_{oc} K_{oc} Sludge1 =1873 L/kg_{oc} K_{oc} Sludge2 = 993 L/kg_{oc}	$K_{oc,sludge}$ < 10000 L/kg does not trigger terrestrial testing
Ready Biodegradability Test	OECD 301	5 – 14%, not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 Sandy Sediment 2 = Silty Clay Loam	OECD 308	DT50, whole system = 0.66 / 0.74 d % shifting to sediment = 77 / 80% CO_2 = 11% / 2% NER = 34% / 44% Transformation products	DT_{50s} at 12°C triggers sediment testing at test end at test end

		>10% = 3, TP1 = 10 / 10% TP2 = 1% / 2% TP3 = N/A / 15%			 at test end at test end at test end
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	EC_{10}	0.71	µg/L	Growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC	1.1	µg/L	Growth
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	0.79	µg/L	Growth (length)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	⩾ 10	µg/L	Respiration
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	N/A		
Sediment dwelling organism/ Chironomus riparius	OECD 218	NOEC	787	mg/k g_{dw}	

The highest risk ratio for ribociclib has been found for sediment compartments with 0.118. Based on the available information on partition behavior and adsorption to sludge and soil, ribociclib is neither expected to bioaccumulate, nor to show any significant transfer to sludge and soil.

2.2.4. Discussion on non-clinical aspects

The current extension of indication application aims to treat early breast cancer in an adjuvant setting and would need to follow ICH M7 guidance for non-clinical development. The non-clinical development supporting the initial MA was conducted according to ICH S9 as ribociclib was intended for the treatment of advanced breast cancer. The N-nitrosoribociclib impurity (N-NRib) is present in trace amounts in ribociclib succinate drug substance and in Ribociclib 200 mg film-coated tablet. N-NRib was tested in three separate Ames tests, including a test applying enhanced Ames test conditions, all concluding that N-NRib did not induce mutations under the test conditions. However, N-NRib was determined to be mutagenic in an in vivo transgenic rodent (TGR) gene mutation assay (Muta™Mouse study). N-NRib limits need to be controlled using the carcinogenic potency categorization approach (CPCA) by applying a maximum acceptable intake (AI) of 400 ng/day (category 3).

The applicant proposed changes to the quality module in a separate procedure (EMEA/H/C/004213/II/54/G) to include measures to minimize the formation of the N-NRib impurity and to ensure control of N-NRib in compliance with the acceptable intake of 400 ng/day for early breast cancer and considering a Maximum Daily Dose (MDD) of 400 mg for the proposed early breast cancer indication.

In order to ensure the N-NRib content remains below the acceptable intake throughout its shelf-life, changes are made to the storage conditions and shelf-life. The product information has been updated accordingly.

This includes a restriction in shelf life and storage conditions from "36 months without special conditions"

to "refrigerated for up to 10 months at the pharmacy + up to 2 months below 25 °C with the patient. Information on the updated storage conditions are included in the PI and will be disseminated via a Direct Healthcare Professional Communication (DHPC).

The ERA initially submitted in the context of the initial MAA has been updated by means of newly calculated Predicted Exposure Concentrations (PECs), which are based on prevalence data for the target indication.

2.2.5. Conclusion on the non-clinical aspects

In the context of the extension of the indication to early breast cancer setting, additional data were provided to assess the potential mutagenicity of the nitrosamine impurity (N-NRib) in line with ICH M7. Risk mitigation measures were set up including storage conditions amendment, Reference is made to EMEA/H/C/004213/II/0054/G for quality aspects. The product information was amended to reflect: Shelf life: 12 months. Special precautions of storage: Pharmacy: store in a refrigerator (2ºC-8ºC) for up to 10 months. Patient: Store below 25ºC for up to 2 months. Store in original package.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of ribociclib. Ribociclib should be used according to the precautions stated in the SmPC to minimize any potential risks 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 MAH.

The MAH 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

Study CLEE011 no. Status	Study design/ Study description/ Objectives	Study population (No. of patients on ribociclib)	Treatment Details (Drug, Dose, Frequency, Duration, Formulation)	PK sampling timepoints (PAS)
[Study O12301C Primary Analysis CSR] Ongoing NATALEE	Phase III, randomized, open-label/Study of ribociclib in combination with NSAI/Safety, efficacy, and PK	Pre- and postmenopausal women, plus men, with HR-positive, HER2-negative eBC (N=2549 (patients randomized)/2526 treated)	Ribociclib 400 mg orally QD on Days 1 to 21 of a 28 day cycle (up to 36 months of treatment) Endocrine therapy (NSAI): Letrozole: 2.5 mg orally QD.[b] given continuously or anastrozole 1 mg orally QD [b] given continuously (plus goserelin 3.6 mg subcutaneously once every 4 weeks in premenopausal women, and men) (up to 60 months of treatment) Formulation: Tablet 200 mg	Sampling time points: Pre-dose, 2 and 4 hr post dose (N=108)

Study CLEE011 no. Status	Study design/ Study description/ Objectives	Study population (No. of patients on ribociclib)	Treatment Details (Drug, Dose, Frequency, Duration, Formulation)	PK sampling timepoints (PAS)
[Study A2207 Primary Analysis CSR] Ongoing AMALEE	Phase II, randomized, open-label/Study of ribociclib in combination with NSAI/Safety, efficacy, and PK	Pre- and postmenopausal women with HR-positive, HER2-negative advanced (i.e. loco-regionally recurrent or metastatic) breast cancer (N=376)	Ribociclib 400 mg, 600 mg orally QD 3 weeks on/1week off (until disease progression) Endocrine therapy (NSAI): Letrozole 2.5 mg orally QD.[b] given continuously or anastrozole: 1 mg orally QD.[b] given continuously (plus goserelin: 3.6 mg subcutaneously once every 4 weeks in premenopausal women) Formulation: Tablet 200 mg	400 mg dose: N=167 (PAS) For patients on extensive PK collection: C1D15: 0, 2, 4, 6, 24 hr (N=20) For patients on non-extensive PK collection: C1D15: 0, 2, 4 hr 600 mg dose: (N=168) For patients on extensive PK collection: C1D15: 0, 2, 4, 6, 24 hr (N=16) For patients on non-extensive PK collection: C1D15: 0, 2, 4 hr
Data cut-offs: Study O12301C: 11-Jan-2023; Study A2207: 11-Jun-2021 Source: [Study O12301C Primary Analysis CSR], [Study A2207 Primary Analysis CSR]				

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

- PK data of ribociclib and/or its combination partners from Study CLEE011O12301C (NATALEE). A Phase III study to evaluate the efficacy and safety of ribociclib 400 mg in combination with ET (NSAI; anastrozole or letrozole) versus ET alone as an adjuvant treatment in pre- and postmenopausal women plus men with HR-positive, HER2-negative eBC.
- PK data of ribociclib from Study CLEE011A2207 (hereafter A2207 or AMALEE), an open-label, randomized, Phase II study to evaluate the safety and efficacy of ribociclib 400 mg + NSAI/AI (letrozole or anastrozole) vs ribociclib 600 mg + AI (letrozole or anastrozole) in the treatment of pre- and postmenopausal women with HR-positive, HER2-negative aBC.
- An updated population PK (popPK) analysis using Study O12301C data, comparison of PK data of Study O12301C and historical studies, updated PK-QT analysis of pooled clinical data, exposure-efficacy, exposure-neutropenia analyses of Study O12301C.
- Drug-drug interaction data based on PBPK report DMPK R2300859 which form the basis for the updated assessment of drug-drug interaction (DDI) at the dose of 400 mg.

2.3.2. Pharmacokinetics

Introduction

A new oral dose of 400 mg once daily for 21 days followed by 7 days off treatment, repeated for 3 years or until disease recurrence or unacceptable toxicity, is proposed for early breast cancer in this application, supported primarily by data from Study O12301C and Study A2207. For reference, the recommended dose in the currently approved indications is 600 mg (three 200 mg film coated tablets) of ribociclib once daily.

Ribociclib is eliminated primarily via CYP3A4 mediated hepatic metabolism. At 600 mg dose ribociclib is a strong time-dependent CYP3A4 inhibitor with auto-inhibition leading to time-dependent pharmacokinetics. Co-administration of the strong CYP3A4 inhibitor ritonavir (100 mg twice daily for 14 days) with a single

400 mg dose of ribociclib increased ribociclib AUCinf and Cmax in healthy subjects 3.2 and 1.7-fold, respectively, compared to a single 400 mg ribociclib dose given alone. Cmax and AUClast for LEQ803 (a prominent metabolite of ribociclib accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively.

At the time of MAA, it was concluded that the contribution of CYP3A4 to the overall elimination is likely smaller at steady state than after a single dose due to time-dependent auto-inhibition of the CYP3A4-mediated metabolism of ribociclib. Thus, in the ritonavir study the effect of ritonavir on ribociclib at steady state might have been overestimated. The effect of a strong and moderate CYP3A4 inhibitors on ribociclib at steady state was therefore simulated using physiologically based pharmacokinetic modelling (PBPK) to inform on dose reductions needs. The same model is updated and proposed to be used here to inform on interactions in early breast cancer patients.

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

Bioanalysis

The concentrations of ribociclib and its metabolite LEQ803 in K3EDTA plasma was determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method was first validated (report DMPKR1300147), and was later re-validated, including a cross-validation of the two sites (DMPKR1300457). The method was transferred and revalidated (DMPK R1600666a) before study sample analysis of both study A2207 and O12301C.

Population PK analysis for Study O12301C

Objectives

The objectives of the popPK analysis were:

- To simulate ribociclib PK in patients in Study O12301C based on the final popPK model and to compare it with the observed PK data;
- To generate individual post hoc longitudinal trough concentrations (Ctrough) of ribociclib in patients in Study O12301C to support the exposure-efficacy analysis of Study O12301C;
- To provide summary of popPK-predicted PK metrics for patients on 400 mg in Study O12301C to support the PK-QT analysis (Cmax at steady-state).

Data

The PopPK analysis was based on PK observations measured in Study O12301C. In Study O12301C, approximately 130 patients from the Investigational arm were to be considered as the PK subset. Plasma samples for ribociclib determination were to be obtained from these patients at the following time points on Day 15 of Cycle 1: pre-dose, 2h post-dose (± 15 min) and 4h post-dose (± 30 min).

The final PopPK dataset included 348 concentrations from 123 patients. The baseline covariates in these patients are summarized in *Table 9*.

Table 9 Distribution of intrinsic factors in popPK dataset

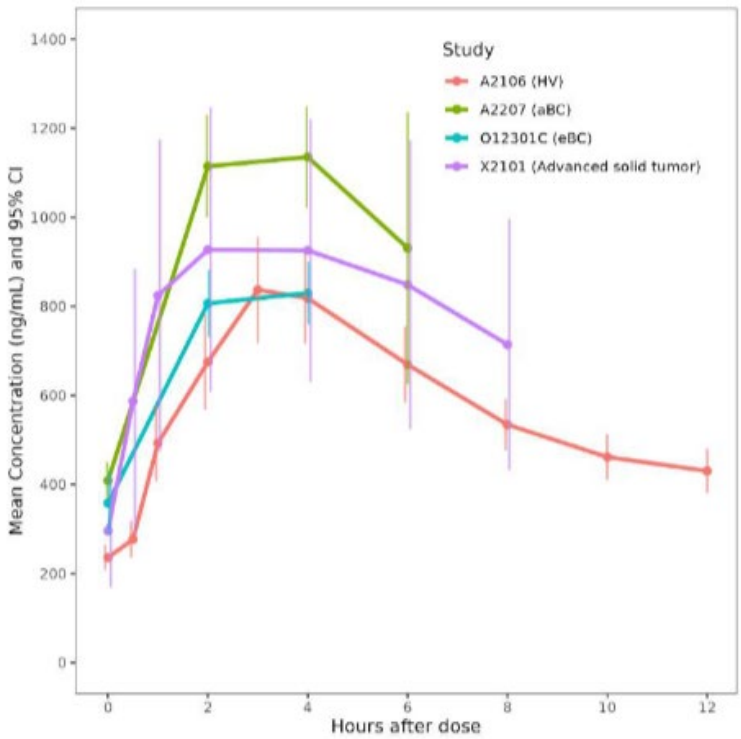
Covariate	Category	N
BW#	<50kg	8
	50-60kg	24
	60-70kg	34
	70-80kg	26
	80-90kg	19
	>=90kg	12
Menopausal status	Premenopausal women and men	42
	Postmenopausal women	81
Anatomic stage group	Stage group II	68
	Stage group III	55

#: Subjects with missing records were excluded from the summary.

Source script: vob/CLEE011O/mas/mas_2/model/pgm_001/MT_86333_NATALEE_submission/scripts/Task_01_Data_transfer.R; Source file: vob/CLEE011O/mas/mas_2/model/pgm_001/MT_86333_NATALEE_submission/outputs/table_6_3_demographics.csv

A summary of the observed ribociclib concentrations from Study O12301C compared to subjects from other parts of the clinical development programme are shown in *Figure 1*.

Figure 1 Steady-state mean concentration of ribociclib in eBC, aBC, and advanced cancer patients and HV at the dose of 400 mg ribociclib (PK-Safety Set)



Data included steady-state doses from studies: A2106 (Day 10), X2101 (Day 18/Day 21), A2207 (Cycle 1 Day 15), O12301C (Cycle 1 Day 15)

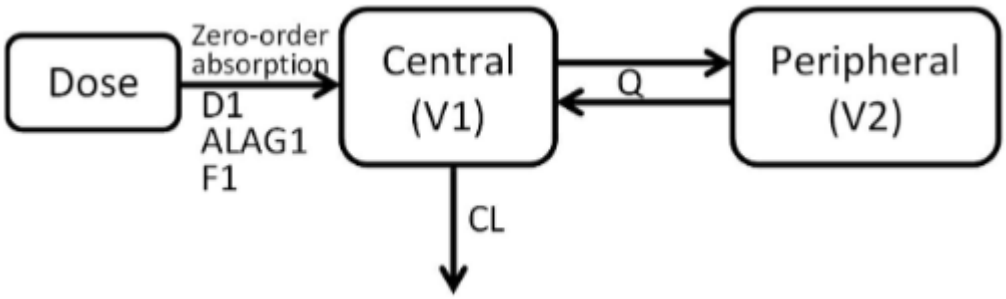
Methods

The popPK model from the previous submission (initial MA, EMEA/H/C/4213) was first updated based on the observed PK data collected from the 123 patients included in the PK analysis dataset. No pooling

between studies was performed in the popPK analysis for Study O12301C. The analysis was performed using Monolix Suite version 2021R.

The popPK model from the previous submission (initial MA, EMEA/H/C/4213) was a two-compartment model with delayed zero-order oral absorption, using linear clearance from the central compartment. The model included dose as a covariate on clearance, inter-compartment clearance, and peripheral volume, and BW on intercompartmental clearance and peripheral volume.

Figure 2 Structure of PopPK model



A reduced model development scheme was applied to describe the PK data in O12301C. The same structure as the previous model was assumed. A base model was defined, where all population parameters were fixed to the previously estimated value. A sensitivity analysis was then performed by estimating one by one all population parameters (including fixed effects, random effect variances and residual variability variances), to identify the closest model which would describe PK in the eBC population.

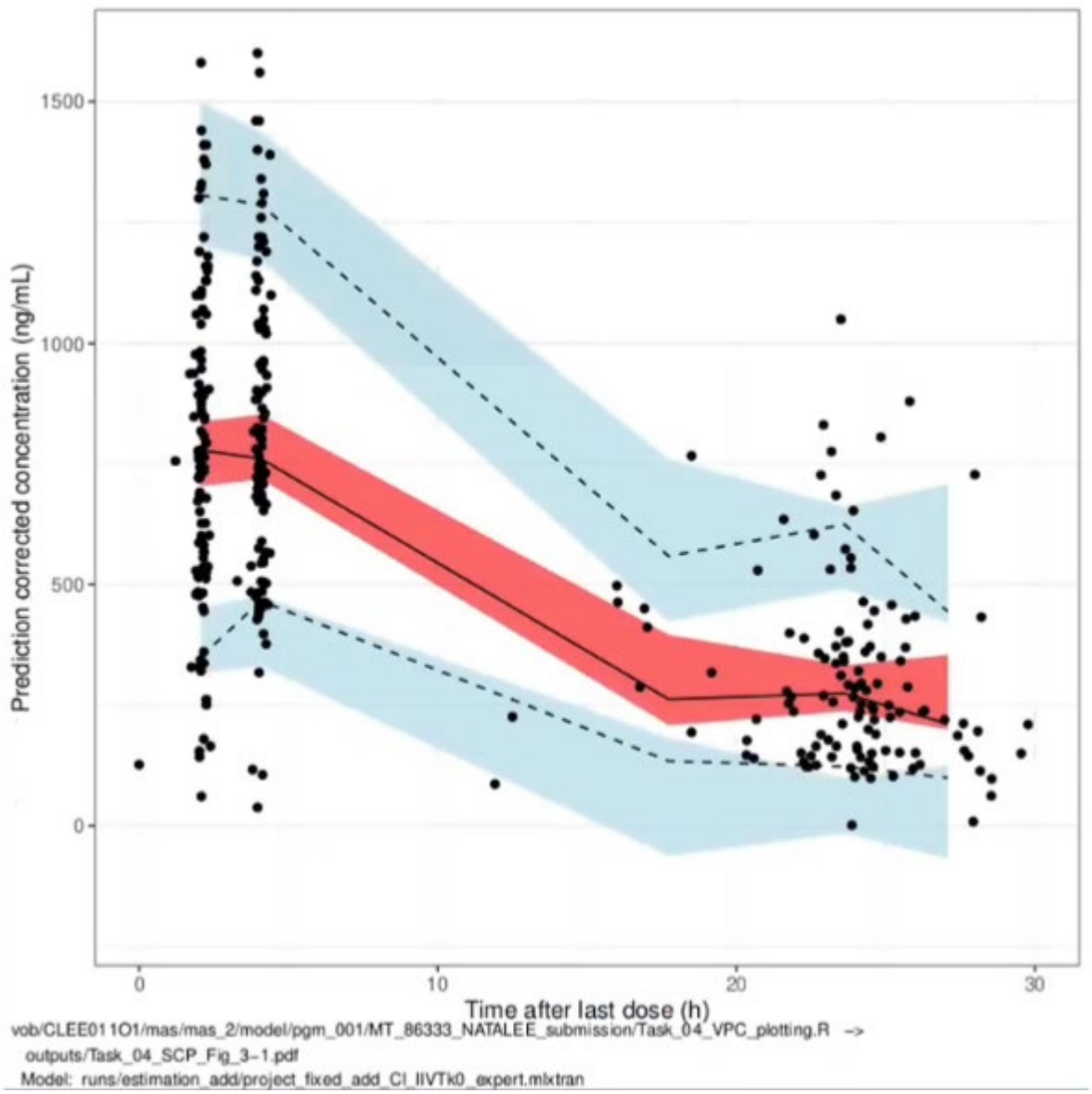
The predictive performance of the PopPK model was evaluated using a visual predictive check (VPC).

The popPK model was updated to describe the lower exposure observed in patients with eBC in Study O12301C in comparison with aBC patients. In the updated popPK model, inter-individual variability was included in the parameter describing the zero-order absorption process (Tk0), along with re-estimation of the clearance parameter. The residual error model was also adjusted to reflect the new study data (the residual error distribution was modified from constant in the log-normal space to constant in the normal space. Mathematically, this is equivalent to changing the residual error model from proportional to additive.). The model simulations (prediction-corrected VPCs) vs observed data are presented in Figure 3. The empirical percentiles (lines) are within the prediction interval of each corresponding theoretical percentiles (areas), indicating the updated popPK model describes data from Study O12301C

Results

The population mean estimate of the apparent clearance of ribociclib at the 600 mg dose was 32.7 L/hr (95% CI: 30.1 – 35.6) in patients with eBC, approximately 19% higher than that in aBC (26.8; 95% CI: 25.8 - 27.7). At a 400 mg dose, population mean estimate of the apparent clearance of ribociclib in patient with eBC was 38.4 L/hr (95% CI: 35.5 - 41.9). Based on the updated popPK model, the estimated population mean steady-state CL/F in eBC patients is approximately 20% higher than that in aBC patients at the dose level of 400 mg (38.4 and 31.5 L/hr, respectively) as well as at the dose level of 600 mg (32.7 and 26.8 L/hr, respectively).

Figure 3 Prediction-corrected visual predictive check (VPC) of the updated PopPK model compared with observed PK concentrations in Study O12301C.



Dots represent the observed concentrations in the PK-iDFS dataset. Upper and lower borders of the blue area represent the 90% CI of the 5th and 95th percentiles of the simulations, while the red area represents the 90% CI of the median. Similarly, the upper and lower dashed line represent the 5th and 95th percentile of the observations, while the solid line represents the median of the observations. The simulations are based on 500 replicates.

Study A2207

PK data are available from study A2207. The purpose of the study was to evaluate if the reduced dosing regimen of 400 mg in combination with an NSAI maintains the efficacy while decreasing the risk of QTc prolongation as well as the frequency of other adverse events in pre- and postmenopausal women with HR-positive, HER2-negative aBC who have received no prior therapy for advanced disease. The study consisted of two arms where arm 1 had 400 mg ribociclib while arm 2 had 600 mg ribociclib. In both ribociclib was taken once daily day 1 to 21, with 7 days off within a 28 day cycle and in combination with endocrine therapy. Extensive PK sampling was performed in approximately 20 patients per arm on C1D15, with sparse sampling in the remaining patients.

Strong inhibitors or inducers of CYP3A4/5 were prohibited in the study, while moderate inhibitors or inducers of CYP3A4/5 were to be used with caution.

The study included 376 female patients randomised 1:1. PK data were available for 167 subjects in the 400 mg group and 168 in the 600 mg group. 162 subjects of the 400 mg did not require any dose reduction, while 26 reduced their dose once. In the 600 mg group, 113 patients did not require a dose reduction, while 57 required one dose reduction and 17 required two. There were no protocol deviations affecting PK. PK parameters in the subjects with extensive sampling are presented in *Table 10*.

Table 10: Ribociclib PK parameters on C1D15 – Study A2207

Dose group	Statistics	Cmax (ng/mL)	Tmax (h)	AUC0-24h (ng×h/mL)	AUClast (ng×h/mL)	Cmin (ng/mL)	CL/F (L/h)	Vz/F (L)
Ribociclib 400 mg (N=20)	n	20	20	17	19	19	17	17
	Mean (SD)	1240 (739)	N/A	18700 (11600)	16800 (11700)	347 (314)	26.7 (9.70)	468 (162)
	CV%	59.5	N/A	62.2	69.3	90.5	36.3	34.6
	Geo-mean	1080	N/A	16400	13500	253	24.4	438
	Geo-CV%	57.8	N/A	51.8	86.0	101.4	51.8	41.3
	Median	983	2.08	12300	12100	218	32.4	472
	Min-max	353-3070	1.83-4.38	11200-46100	1620-44400	29.3-1200	8.68-35.7	208-718
Ribociclib 600 mg (N=16)	n	16	16	13	15	15	13	13
	Mean (SD)	1740 (918)	N/A	31600 (14300)	28500 (15100)	691 (405)	23.3 (11.9)	655 (601)
	CV%	52.7	N/A	45.3	53.1	58.5	51.1	91.7
	Geo-mean	1500	N/A	28600	24100	584	21.0	523
	Geo-CV%	67.0	N/A	50.0	74.1	71.2	50.0	69.6
	Median	1640	4.00	29800	26100	525	20.1	460
	Min-max	374-3290	1.83-23.8	11100-58800	4240-58300	111-1500	10.2-53.9	225-2540

n = number of patients with corresponding evaluable PK parameters.
Ribociclib 400 and 600 mg dose groups consist of all patients who provided evaluable parameters after receiving at least 10 consecutive daily ribociclib doses of 400 and 600 respectively, immediately prior to and on the PK collection day.
Source: Table 14.2-4.2

Following daily oral administration of ribociclib with 3 weeks on/1 week off, the median (range) of Tmax on C1D15 was 2.1 (1.8-4.4) h and 4 (1.8-23.8) h for the ribociclib 400 mg and 600 mg arms, respectively. The geometric mean of ribociclib Cmax and AUC0-24h at C1D15 were approximately 28% and 43% lower in the ribociclib 400 mg arm as compared to the 600 mg arm (Cmax 1080 vs 1500 ng/mL and AUC0 24h 16400 vs. 28600 ng×h/mL).

Special populations

Based on the dedicated hepatic impairment study A2109 (submitted at the time of MAA) with 400 mg ribociclib, the AUC for ribociclib was increased by 1.32 and 1.29 fold respectively, in patients with moderate and severe hepatic impairment compared to subjects with normal hepatic function.

Pharmacokinetic interaction studies

No new DDI studies are provided as part of this submission. Results of drug-drug interaction studies were assessed in the original MAA submission and are described in the approved SmPC.

Details of PBPK predictions for eBC and aBC populations are summarized in DMPK R2300859 report submitted. The focus lies on the victim interaction with CYP3A4 inhibitors or inducers thus the assessment is limited to that part of the model. SmPC has been updated based on the model.

PBPK report DMPK R2300859

The observed pharmacokinetics (PK) for ribociclib was different in healthy volunteers and metastatic breast cancer patients, mainly due to the lower clearance (CL/F) observed for patients. Therefore, the use of two physiologically based pharmacokinetic (PBPK) population models for healthy volunteers and metastatic breast cancer, described by Samant et al (2020), were combined with the same compound model for ribociclib. Simcyp V22 was used for all simulations, as compared to V18 earlier. The only

changes applied to the ribociclib compound file were the following: the absorption model was changed from ADAM to first order absorption to simplify the model. Consequently, the fa, ka and lag time were adapted from 0.942, 1.052 h-1 and 0 h to values of 1.00, 0.700 h-1 and 1.10 h. The remaining compound files were used unchanged and are provided in the report.

The early breast cancer population, was actually represented by the Simcyp healthy volunteer population file from V22 with some modifications

The Simcyp healthy volunteers population file was modified by reducing the amount of microsomal protein per gram of liver to 12% and the CV for the hepatic CYP3A4 abundance was reduced to 23.8% to match the clinically observed PK variability of ribociclib for both populations. Furthermore, for a metastatic breast cancer population model the hepatic and intestinal CYP3A4 abundance was also reduced to account for the disease-related reduction. The abundance values of these two parameters were reduced by 40% to 82.2 pmol/mg protein and 39.2 pmol/mg protein, respectively, as described in the supporting information of Samant et al (2020).

The PK of ribociclib was predicted following single dose administrations of 150 mg i.v. and 600 mg p.o. to healthy volunteers and multiple dose administration of 400 mg QD to metastatic breast cancer patients (*Table 11*, Figure 4).

Table 11: Predicted and observed PK parameters for ribociclib in healthy subjects or metastatic breast cancer patients

Population	Ribociclib dose regimen[1]	Observed median Tmax (h^{-1}) [3,4]	Predicted median Tmax (h^{-1})	Observed Geometric Mean Cmax (%CV) (ng/mL) [3,4]	Predicted Geometric Mean Cmax (%CV) (ng*h/mL)	Observed Geometric Mean AUC (%CV) (ng*h/mL) [3,4]	Predicted Geometric Mean AUC (%CV) (ng*h/mL)
HV	150 mg SD i.v.	3.52	4.0	347 (22.8)	363 (19.3)	3781 (27.4)	3781 (21.2)
HV	600 mg SD p.o.	2.99	2.45	624 (42.5)	728 (35.9)	9840 (44.4)	8865 (36.5)
Metastatic breast cancer	400 mg QD p.o.	-	2.70	1040 (49.3)	1071 (32.4)	11400 (57.8)	13814 (42.7)

%CV, percent coefficient of variance; HV, healthy volunteer; i.v., intravenous; p.o. per oral; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was either the "adapted healthy volunteer (HV)" or the "metastatic breast cancer patient" population model. Details of the trial design can be found in Table 3-1.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

[3] observed HV ribociclib Cmax and AUCinf at day 1 for a 150 and 600 mg SD dose taken from (CLEE011A2117)

[4] observed HV ribociclib Cmax and AUCtau at day 18/21 for a 400 mg QD dose taken from (CLEE011X2101)

Figure 4: Simulated and observed mean pharmacokinetic profiles of ribociclib administered p.o. (left) or i.v. (right) to healthy volunteers. Simulated mean ribociclib concentrations (black line), 5th and 95th percentiles (dashed grey lines), observed mean concentrations (open circles) for ribociclib 600 mg single dose p.o.

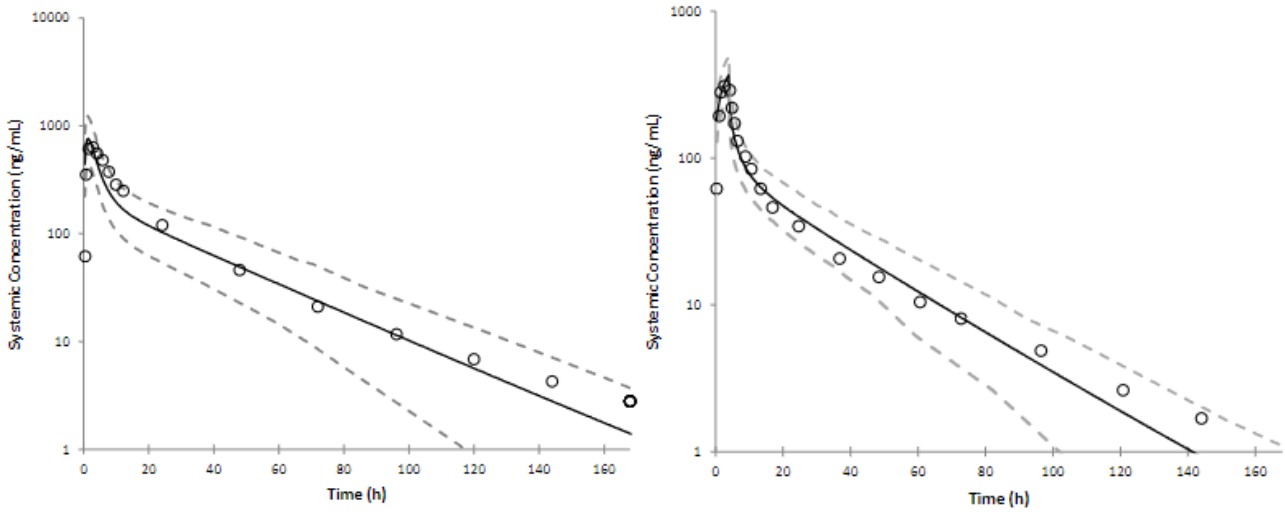
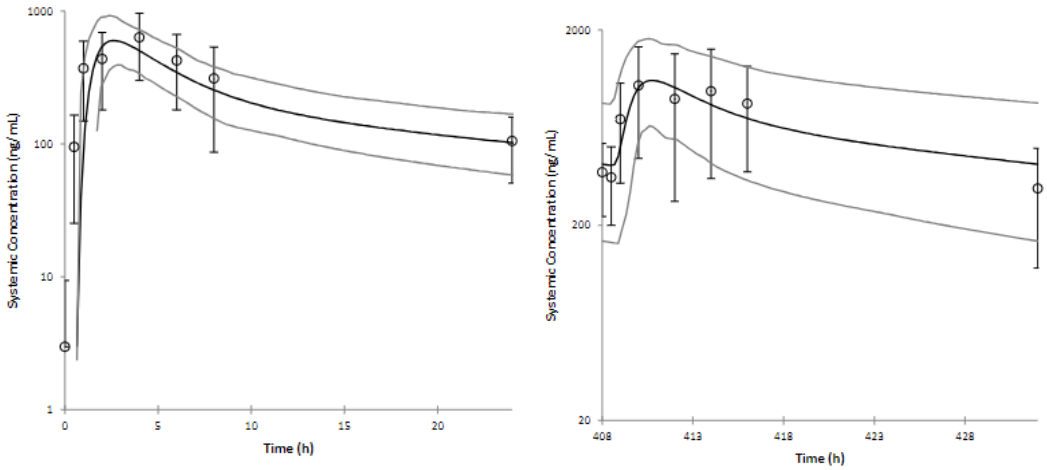


Figure 5: Simulated (metastatic breast cancer patients) and observed mean pharmacokinetic profiles of ribociclib administered to metastatic breast cancer patients after on day 1 (left) and on day 18 (right)



Ribociclib as a perpetrator had been previously qualified (Kisqali iMA). The model in V22 predicted the interaction with CYP3A4 by matching the observed AUC and Cmax ratios for midazolam of 3.75 and 2.05, respectively (predicted AUC ratio: 4.18, Cmax ratio: 2.28, *Table 12*).

The DDI effect of the strong CYP3A4 inhibitor ritonavir was predicted with observed AUC and Cmax ratios of 3.21 and 1.67 and predicted AUC and Cmax ratios of 3.16 and 1.40, respectively (*Table 12*). Finally, the induction effect of rifampicin on ribociclib was reasonably described. The observed AUC and Cmax ratios were 0.107 and 0.190 and the predicted AUC and Cmax ratios were 0.231 and 0.447, respectively (*Table 12*).

Table 12: Predicted and observed PK parameters for interactions of midazolam, ribociclib, ritonavir and rifampicin in healthy subjects

Perpetrator dose regimen	Victim dose regimen	Source	Geometric Mean Cmax (%CV) (ng/mL) of victim drug Not inh./inh.	Observed Geometric Mean AUC (%CV) (ng*h/mL) of victim drug Not inh./inh.	Victim drug geometric Mean Cmax ratio (90% CI)	Victim drug geometric Mean AUC ratio (90% CI)
Ribociclib 400 mg QD for 8 days	Midazolam 2 mg SD at day 8	Observed [3] Predicted	7.85 (28.4)/16.1 (22.6) 7.46 (66.6)/17.0 (59.3)	17.7 (26.9)/66.4 (33.3) 20.5 (67.3)/85.8 (90.1)	2.05 (1.88, 2.23) 2.28 (2.18, 2.38)	3.75 (3.41, 4.11) 4.18 (3.84, 4.55)
Ritonavir 100 mg BID for 13 days	Ribociclib 400 mg SD day 2	Observed [4] Predicted	357/597 469 (36.0)/657 (31.9)	5840/18700 5395 (34.6)/17062 (35.4)	1.67 (1.52, 1.84) 1.40 (1.38, 1.42)	3.21 (2.95, 3.49) 3.16 (3.04, 3.29)
Rifampicin 600 mg QD for 13 days	Ribociclib 600 mg SD day 5	Observed [4] Predicted	565/107 671 (35.1)/300 (59.2)	8940/953 8304 (37.1)/1922 (62.2)	0.190 (0.164, 0.219) 0.447 (0.422, 0.474)	0.107 (0.0945, 0.120) 0.231 (0.214, 0.249)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; HV, healthy volunteer; inh, inhibited; QD, once a day; SD, single dose

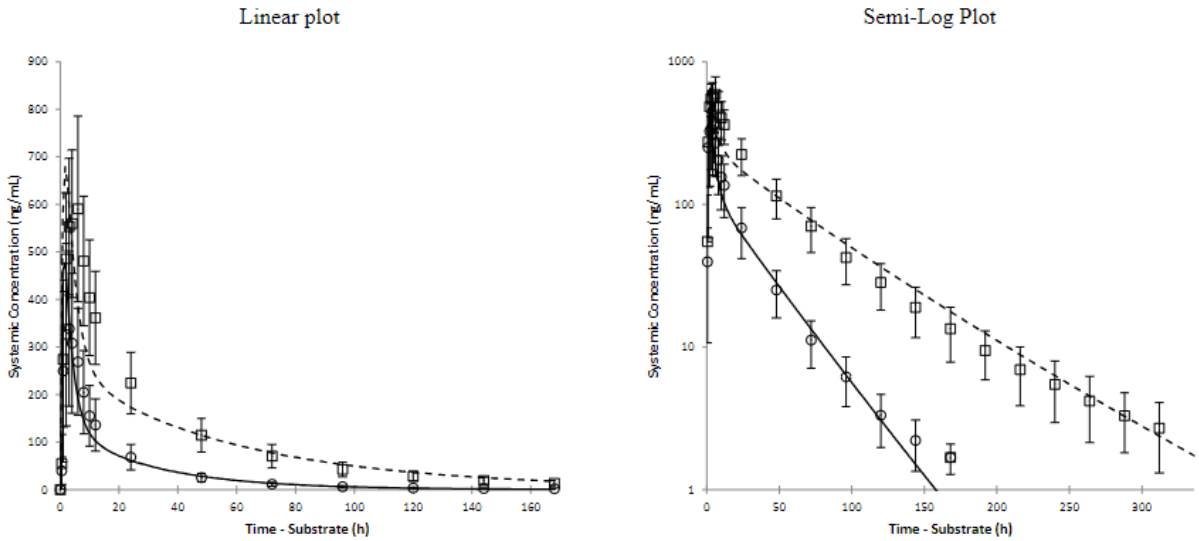
[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 50% female for the midazolam and ritonavir studies and 20.8% for the rifampicin study. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-2 and Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib and midazolam single dose.

[3] observed HV midazolam Cmax, AUCinf and their ratios at day 8 taken from (CLEE011A2106)

[4] observed HV ribociclib Cmax, AUCinf and their ratios taken from (CLEE011A2101)

Figure 6: Simulated and observed mean pharmacokinetic profiles of ribociclib administered without and with ritonavir 100 mg b.i.d. to healthy volunteers. Simulated mean ribociclib concentrations with and without ritonavir (black/dashed line), observed mean concentrations with and without ritonavir (open circles/squares) for ribociclib 400 mg single dose p.o.



When using the adapted healthy volunteer population file, the plasma concentrations for the time points 2, 4 and 24 h on day 18 of the NATALEE study in early breast cancer were predicted with prediction error (PE) values less than 7% (

Table 13,

Figure 7). The simulations using the metastatic breast cancer patient population file overpredicted the plasma concentrations (Figure 8, PE >22%).

Table 13: Day 18 predicted (healthy subject or metastatic breast cancer population) and observed ribociclib PK after ribociclib 400 mg QD in early breast cancer patients (NATALEE)

Parameter	Observed value for 2 h time point	Predicted value for 2 h time point	Observed value for 4 h time point	Predicted value for 4 h time point	Observed value for 24 h time point	Predicted value for 24 h time point
Number of included patients	105	100	113	100	105	100
Accurate time (h)	410.08 ± 0.15	409.97	412.07 ± 0.15	411.91	432.00 ± 2.01	432.00
Plasma concentration (ng/mL)	815 ± 379	HV: 871 ± 342 CP: 1002 ± 377	819 ± 366	HV: 869 ± 307 CP: 1024 ± 333	325 ± 272	HV: 306 ± 183 CP: 411 ± 218
Concentration prediction error (%)[3]	-	HV: 6.87 CP: 22.9	-	HV: 6.11 CP: 25.0	-	HV: -5.85 CP: 26.5

CP, cancer patient; HV, healthy volunteer; PE, prediction error; QD, once a day

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was either the "adapted healthy volunteer (HV)" or the "metastatic breast cancer patient" model. Details of the trial design can be found in Table 3-1.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

[3] Prediction error (PE) calculated as PE = (simulated value – observed value) / observed value × 100

Figure 7: Simulated (using the adapted HV population model) PK profiles and observed mean (left) or individual (right) subject concentrations of ribociclib administered to early breast cancer patients (adjuvant therapy) for 18 days. Simulated mean ribociclib concentrations (black line), 5th and 95th percentiles (dashed grey lines), observed individual concentrations (open circles) for ribociclib 400 mg once daily p.o. day 18

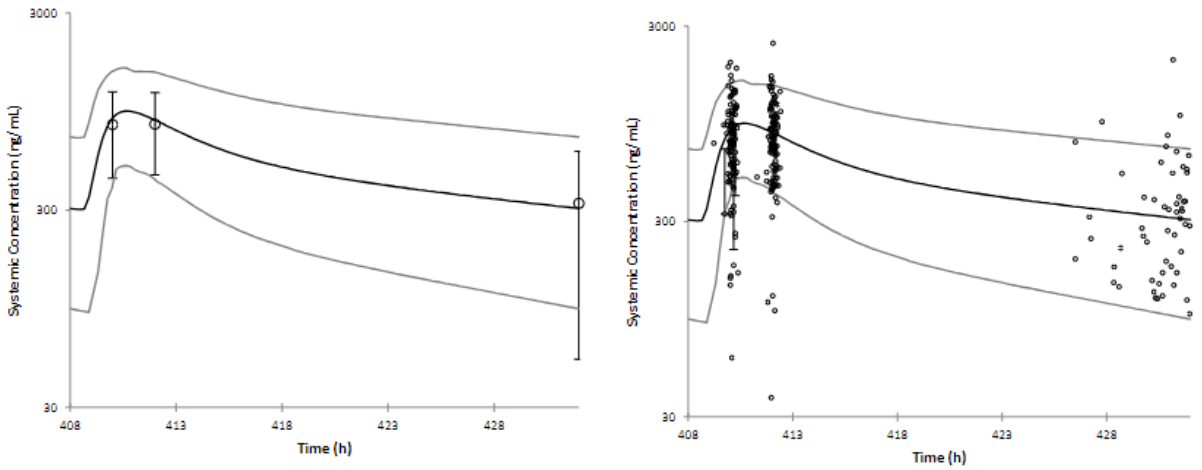
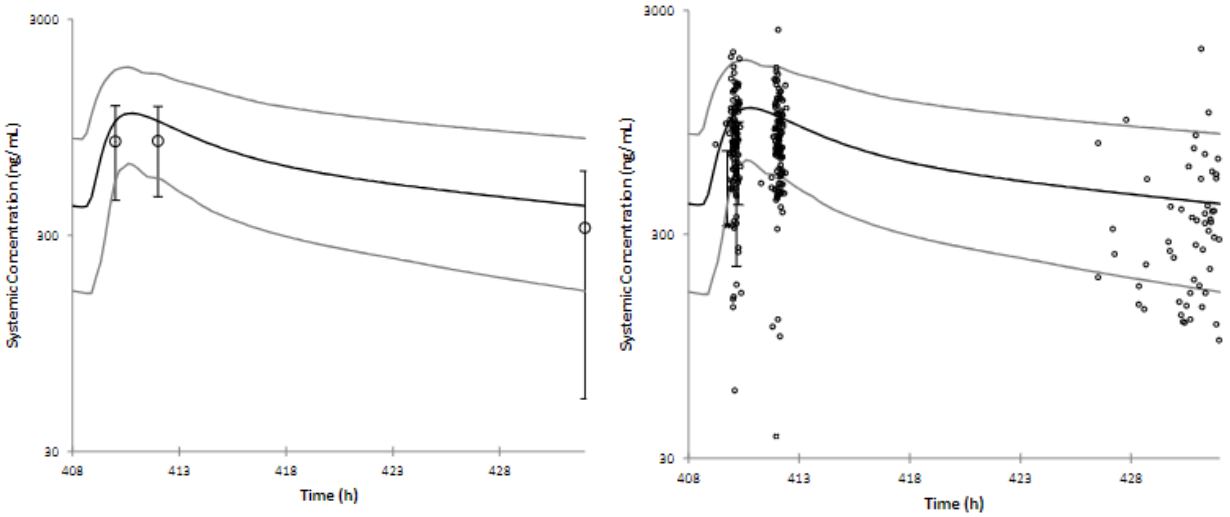


Figure 8: Simulated (using the metastatic breast cancer population model) PK profiles and observed mean (left) or individual (right) subject concentrations of ribociclib administered to early breast cancer patients (adjuvant therapy) for 18 days. Simulated mean ribociclib concentrations (black line), 5th and 95th percentiles (dashed grey lines), observed mean concentrations (open circles) and standard deviation (error bars) for ribociclib 400 mg once daily p.o. on day 18



Simulations

Numerous scenarios have been simulated using the adapted healthy population file with CYP3A4 inhibitors (Table *14*) and inducers (In the presence of the strong CYP3A4 inducer rifampicin the AUC and Cmax ratios of ribociclib (400 mg SD) were predicted to be 0.200 and 0.398, respectively, in HV. In the presence of the moderate CYP3A4 inducer efavirenz slightly less DDI was predicted with ribociclib AUC and Cmax ratios of 0.314 and 0.550, respectively.

Table 15) and similarly using the metastatic breast cancer population file (*Table 16* and *Table 17*). Co-administration of the strong CYP3A4 inhibitor ritonavir with 400 mg ribociclib resulted in ribociclib AUC and Cmax ratios of 1.84 and 1.47, respectively. Similar ribociclib AUC was predicted when administered as single dose (18966 ng*h/mL) or at steady-state (19401 ng*h/mL) when co-administered with ritonavir, which was slightly lower than the ribociclib AUC following a 600 mg QD dose at steady-state (23800 ng*h/mL) without ritonavir co-medication. For the moderate CYP3A4 inhibitor erythromycin a ribociclib (400 mg QD) AUC and Cmax increase of 1.23- and 1.13-fold was predicted.

Table 14: Predicted exposure of ribociclib when administered with CYP3A4 inhibitors – healthy subjects

Perpetrator	Source	Ribociclib dose regimen [1]	Inhibition status	Geometric Mean Cmax (%CV) (ng/mL)	Geometric Mean AUC (%CV) (ng*h/mL)	Geometric Mean Cmax ratio (90%CI)	Geometric Mean AUC ratio (90% CI)
Ritonavir 100 mg BID for 14 days	simulated	600 mg SD on day 8	- inhibitor + inhibitor	807 (29.3) 1163 (25.2)	9646 (35.9) 30250 (38.2)	1.44 (1.42, 1.46)	3.14 (3.00, 3.28)
Ritonavir 100 mg BID for 8 days	simulated	600 mg QD for 8 days	- inhibitor + inhibitor	1496 (35.2) 1984 (28.9)	18696 (46.5) 29114 (35.5)	1.33 (1.29, 1.36)	1.56 (1.50, 1.62)
Ritonavir 100 mg BID for 14 days	observed	400 mg SD on day 2	- inhibitor + inhibitor	357 597	5840 18500	1.67 (1.52, 1.84)	3.21 (2.95, 3.49)
Ritonavir 100 mg BID for 14 days	simulated	400 mg SD on day 2	- inhibitor + inhibitor	518 (28.6) 769 (24.6)	5749 (33.5) 18966 (33.6)	1.40(1.38, 1.40)	3.14 (3.03, 3.27)
Ritonavir 100 mg BID for 8 days	simulated	400 mg QD for 8 days	- inhibitor + inhibitor	900 (35.5) 1322 (28.9)	10523 (47.1) 19401 (35.5)	1.47 (1.43, 1.51)	1.84 (1.76, 1.93)
Ritonavir 100 mg BID for 14 days	simulated	200 mg SD on day 2	- inhibitor + inhibitor	249 (28.7) 388 (25.3)	2641 (32.6) 10079 (38.2)	1.56 (1.53, 1.58)	3.82 (3.64, 4.00)
Ritonavir 100 mg BID for 8 days	simulated	200 mg QD for 8 days	- inhibitor + inhibitor	375 (33.5) 661 (28.9)	3855 (42.5) 9696 (35.5)	1.76 (1.72, 1.82)	2.51 (2.40, 2.63)
Erythromycin 500 mg BID for 8 days	simulated	600 mg SD on day 8	- inhibitor + inhibitor	807 (29.3) 987 (28.9)	9659 (36.0) 16272 (42.8)	1.22 (1.21, 1.24)	1.68 (1.63, 1.74)
Erythromycin 500 mg BID for 8 days	simulated	600 mg QD for 8 days	- inhibitor + inhibitor	1496 (35.2) 1617 (33.3)	18696 (46.5) 21168 (43.0)	1.08 (1.07, 1.09)	1.13 (1.12, 1.14)
Erythromycin 500 mg BID for 8 days	simulated	400 mg SD on day 8	- inhibitor + inhibitor	521 (29.1) 648 (29.0)	5862 (34.3) 10285 (42.6)	1.24 (1.23, 1.26)	1.75 (1.69, 1.82)
Erythromycin 500 mg BID for 8 days	simulated	400 mg QD for 8 days	- inhibitor	900 (35.5)	10523 (47.1)	1.13 (1.12, 1.14)	1.23 (1.21, 1.24)
			+ inhibitor	1021 (33.7)	12912 (44.0)		
Erythromycin 500 mg BID for 8 days	simulated	200 mg SD on day 8	- inhibitor + inhibitor	249 (28.7) 317 (29.0)	2642 (32.7) 4787 (42.1)	1.27 (1.26, 1.29)	1.81 (1.74, 1.88)
Erythromycin 500 mg BID for 8 days	simulated	200 mg QD for 8 days	- inhibitor + inhibitor	375 (33.5) 468 (33.5)	3855 (42.5) 5593 (43.9)	1.25 (1.23, 1.26)	1.45 (1.42, 1.48)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

[3] observed ribociclib Cmax and AUCtau at day 18/21 for a 600 mg QD dose: 1820 ng/mL and 23800 ng*h/mL (CLEE011X2101)

In the presence of the strong CYP3A4 inducer rifampicin the AUC and Cmax ratios of ribociclib (400 mg SD) were predicted to be 0.200 and 0.398, respectively, in HV. In the presence of the moderate CYP3A4 inducer efavirenz slightly less DDI was predicted with ribociclib AUC and Cmax ratios of 0.314 and 0.550, respectively.

Table 15: Predicted exposure of ribociclib when administered with CYP3A4 inducers – healthy subjects

Perpetrator	Source	Ribociclib dose regimen [1]	Induction status	Geometric Mean C_{max} (%CV) (ng/mL)	Geometric Mean AUC (%CV) (ng*h/mL)	Geometric Mean C_{max} ratio (90%CI)	Geometric Mean AUC ratio (90% CI)
Rifampicin 600 mg QD for 13 days	observed	600 mg SD on day 5	- inducer + inducer	565 107	8940 953	0.190 (0.164, 0.219)	0.107 (0.0945, 0.120)
Rifampicin 600 mg QD for 13 days	simulated	600 mg SD on day 5	- inducer + inducer	671 (35.1) 300 (59.2)	8318 (37.2) 1922 (62.2)	0.447 (0.422, 0.474)	0.231 (0.214, 0.249)
Rifampicin 600 mg QD for 14 days	simulated	600 mg QD for 14 days	- inducer + inducer	1500 (34.7) 567 (64.7)	18607 (46.2) 3646 (93.3)	0.378 (0.351, 0.407)	0.196 (0.176, 0.218)
Rifampicin 600 mg QD for 14 days	simulated	400 mg SD on day 12	- inducer + inducer	518 (28.6) 206 (53.6)	5753 (33.5) 1149 (59.2)	0.398 (0.374, 0.423)	0.200 (0.185, 0.216)
Rifampicin 600 mg QD for 14 days	simulated	400 mg QD for 14 days	- inducer + inducer	911 (35.6) 311 (60.1)	10633 (48.2) 1813 (77.8)	0.342 (0.318, 0.367)	0.171 (0.155, 0.188)

Rifampicin 600 mg QD for 14 days	simulated	200 mg SD on day 12	- inducer + inducer	248 (28.2) 96.1 (54.2)	2596 (31.9) 520 (59.4)	0.388 (0.364, 0.413)	0.200 (0.185, 0.217)
Rifampicin 600 mg QD for 14 days	simulated	200 mg QD for 14 days	- inducer + inducer	383 (34.4) 124 (56.4)	3986 (45.6) 660 (65.4)	0.324 (0.302, 0.347	0.166 (0.151, 0.181)
Efavirenz 600 mg QD for 14 days	simulated	600 mg SD at day 12	- inducer + inducer	807 (29.3) 450 (36.5)	9659 (36.0) 2967 (44.3)	0.557 (0.537, 0.578)	0.307 (0.288, 0.328)
Efavirenz 600 mg QD for 14 days	simulated	600 mg QD for 14 days	- inducer + inducer	1549 (36.8) 747 (51.0)	19692 (49.4) 5735 (78.7)	0.483 (0.453, 0.514)	0.291 (0.262, 0.324)
Efavirenz 600 mg QD for 14 days	simulated	400 mg SD at day 12	- inducer + inducer	521 (29.1) 286 (36.2)	5866 (34.4) 1842 (43.1)	0.550 (0.530, 0.571)	0.314 (0.295, 0.335)
Efavirenz 600 mg QD for 14 days	simulated	400 mg QD for 14 days	- inducer + inducer	936 (37.2) 421 (47.3)	11189 (50.4) 2907 (67.9)	0.449 (0.424, 0.477)	0.260 (0.236, 0.286)
Efavirenz 600 mg QD for 14 days	simulated	200 mg SD at day 12	- inducer + inducer	249 (28.7) 135 (35.7)	2642 (32.7) 846 (42.1)	0.542 (0.521, 0.563)	0.320 (0.301, 0.341)
Efavirenz 600 mg QD for 14 days	simulated	200 mg QD for 14 days	- inducer + inducer	390 (35.2) 171 (41.2)	4127 (46.3) 1062 (52.6)	0.440 (0.418, 0.463)	0.257 (0.237, 0.279)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

[3] observed ribociclib Cmax and AUCinf at day 1 for a 600 mg SD dose taken from (CLEE011A2117)

Table 16: Predicted exposure of ribociclib when administered with CYP3A4 inhibitors – metastatic breast cancer

Perpetrator	Source	Ribociclib dose regimen [1]	Inhibition status	Geometric Mean Cmax (%CV) (ng/mL)	Geometric Mean AUC (%CV) (ng*h/mL)	Geometric Mean Cmax ratio (90%CI)	Geometric Mean AUC ratio (90% CI)
Ritonavir 100 mg BID for 8 days	simulated	600 mg QD for 8 days	- inhibitor + inhibitor	1685 (32.1) 1990 (28.9)	22656 (40.6) 29241 (35.4)	1.18 (1.16, 1.20)	1.29 (1.26, 1.32)
Ritonavir 100 mg BID for 8 days	simulated	400 mg QD for 8 days	- inhibitor + inhibitor	1054 (32.5) 1326 (28.9)	13643 (41.5) 19490 (35.4)	1.26 (1.24, 1.28)	1.43 (1.39, 1.47)
Ritonavir 100 mg BID for 14 days	simulated	200 mg QD for 8 days	- inhibitor + inhibitor	463 (31.8) 663 (28.9)	5519 (39.9) 9743 (35.4)	1.43 (1.40, 1.46)	1.77 (1.71, 1.83)
Erythromycin 500 mg BID for 8 days	simulated	600 mg QD for 8 days	- inhibitor + inhibitor	1685 (32.1) 1761 (31.1)	22656 (40.6) 24262 (38.8)	1.05 (1.04, 1.05)	1.07 (1.06, 1.08)
Erythromycin 500 mg BID for 8 days	simulated	400 mg QD for 8 days	- inhibitor + inhibitor	1054 (32.5) 1134 (31.3)	13643 (41.5) 15318 (39.3)	1.08 (1.07, 1.08)	1.12 (1.11, 1.13)
Erythromycin 500 mg BID for 8 days	simulated	200 mg QD for 8 days	- inhibitor + inhibitor	463 (31.8) 536 (31.2)	5519 (39.9) 6983 (39.3)	1.16 (1.15, 1.17)	1.27 (1.25, 1.28)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

Table 17: Predicted exposure of ribociclib when administered with CYP3A4 inducers – metastatic breast cancer

Perpetrator	Source	Ribociclib dose regimen [1]	Induction status	Geometric Mean C_{max} (%CV) (ng/mL)	Geometric Mean AUC (%CV) (ng*h/mL)	Geometric Mean C_{max} ratio (90%CI)	Geometric Mean AUC ratio (90% CI)
Rifampicin 600 mg QD for 14 days	simulated	600 mg QD for 14 days	- inducer + inducer	1678 (31.2) 882 (53.6)	22321 (39.3) 7313 (83.3)	0.526 (0.496, 0.557)	0.328, 0.298, 0.360)
Rifampicin 600 mg QD for 14 days	simulated	400 mg QD for 14 days	- inducer + inducer	1055 (31.9) 494 (52.4)	13533 (40.9) 3671 (77.0)	0.468 (0.442, 0.497)	0.271 (0.248, 0.297)
Rifampicin 600 mg QD for 14 days	simulated	200 mg QD for 14 days	- inducer + inducer	468 (31.9) 196 (48.2)	5576 (41.1) 1274 (62.4)	0.418 (0.395, 0.443)	0.229 (0.211, 0.248)
Efavirenz 600 mg QD for 14 days	simulated	600 mg QD for 14 days	- inducer + inducer	1738 (33.6) 1068 (42.9)	23686 (43.1) 10366 (64.6)	0.615 (0.584, 0.646)	0.438 (0.401, 0.477)
Efavirenz 600 mg QD for 14 days	simulated	400 mg QD for 14 days	- inducer + inducer	1090 (34.1) 611 (42.2)	14324 (44.1) 5324 (62.8)	0.561 (0.533, 0.591)	0.372 (0.340, 0.406)
Efavirenz 600 mg QD for 14 days	simulated	200 mg QD for 14 days	- inducer + inducer	481 (33.3) 249 (38.0)	5847 (43.0) 1883 (52.1)	0.517 (0.493, 0.542)	0.322 (0.297, 0.349)

BID, twice a day; CI, confidence interval; %CV, percent coefficient of variance; QD, once a day; SD, single dose

[1] The simulated trials consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and 100% female. The population model used was the "adapted healthy volunteer (HV)" model. Details of the trial design can be found in Table 3-3.

[2] Reported AUC values and ratios were AUCinf for ribociclib single dose and AUCtau for ribociclib at steady-state.

2.3.3. Pharmacodynamics

Mechanism of action

Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling 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).

Primary and secondary pharmacology

2.3.4. PK/PD modelling

Several PK/PD or exposure-response analyses were performed including a PK-QTc, exposure-efficacy and exposure-neutropenia analyses. However, only the PK-QTc analysis is described below.

PK-QTc analysis

The objective of this analysis was to characterize the relationship between the QTcF matched ribociclib concentration and the ΔQTcF with or without combination partners (NSAI (letrozole or anastrozole) and fulvestrant).

In the PK-ECG set of pooled studies, 1297 of 1372 patients (94.5%) were female and the remaining were male (75 patients, 5.5%). Overall median age of patients was 58.0 years (range: 22 to 96), with 8.2%, 60.0%, and 31.8% of patients being < 40 years, 40 to < 65 years, and ≥65 years, respectively. Overall, patients were predominantly non-Asian (87.0%), and the majority of patients (62.4%) had an ECOG PS of 0. The analysis included 1372 patients in total where 117 were eBC patients from Study OC12301C. Studies A220, E2301, F2301, A2301, X2108, X2107, submitted with previous applications, were also included.

The baseline QTcF are summarized in Table 18.

Table 18 Baseline QTcF (PK-ECG)

Statistics	X1101 N=17	X2101 N=152	X2107 N=47	A2301 N=75	E2301 N=203	F2301 N=425	A2207 N=336	O12301C N=117	All patients N=1372
n	17	152	47	75	203	425	336	117	1372
Mean (SD)	417.25 (19.671)	411.42 (18.805)	415.87 (15.068)	414.12 (15.290)	415.70 (17.232)	415.23 (17.095)	407.47 (17.485)	420.13 (16.154)	413.38 (17.600)
Median	415.67	410.17	416.00	413.67	415.00	415.00	406.33	419.00	413.00
Q1-Q3	405.67-430.33	398.00-425.50	405.00-429.00	402.67-424.00	403.67-429.00	403.33-427.33	394.83-419.00	410.00-434.00	401.67-426.33
Min-Max	382.7-454.7	359.0-458.2	378.3-451.7	382.3-451.0	373.7-462.0	362.0-453.0	354.3-463.5	383.0-447.0	354.3-463.5

A standard workflow and model evaluation for QTcF analysis was applied. The effect of covariates such as patient population (eBC vs non-eBC) on QTcF prolongation was assessed.

Patient population (eBC vs non-eBC patients) was found to be statistically significant ($p<0.001$). Patients in eBC population were predicted to have lower ΔQTcF (-5.37 ms) than advanced cancer population at the same ribociclib concentration. All the other covariates evaluated in the previous model (M3/7 QT report)

were retained and the corresponding parameter estimates are consistent between the two models. Using the updated PK-QTcF model, at the geometric mean steady-state Cmax of the ribociclib 400 mg dose in the eBC population with NSAI (letrozole or anastrozole) as combination partner, the estimated mean ΔQTcF was 10.0 ms (90% CI: 8.02, 11.91).

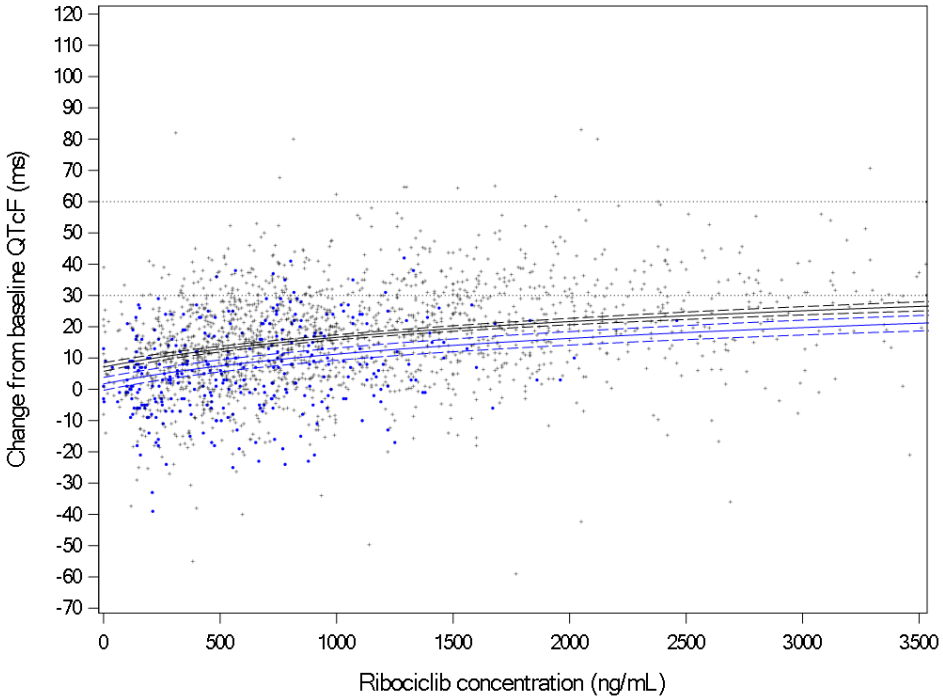
The final model parameters are shown in Table 19.

Table 19 Parameter estimates from PK-QTc model, PK-ECG set

Parameter	Estimate (95% CI)	Standard error
Baseline QTcF-median baseline QTcF	-0.23 (-0.27, -0.19)	0.02
Intercept	1.76 (-0.70, 4.21)	1.25
Log(concentration/median concentration+1)	11.09 (9.51, 12.66)	0.80
Log(concentration/median concentration+1)*Fulvestrant	2.87 (0.62, 5.12)	1.15
Log(concentration/median concentration+1)*NSAI (letrozole or anastrozole)	.	
Log(concentration/median concentration+1)*No combination	4.94 (3.07, 6.80)	0.95
Fulvestrant	-0.60 (-2.86, 1.66)	1.15
NSAI (letrozole or anastrozole)	.	
No combination	-7.84 (-10.25, -5.42)	1.23
Early breast cancer	.	
Non-early breast cancer	5.37 (2.85, 7.90)	1.29

The observed and model-predicted change from baseline vs ribociblib concentration in eBC patients are shown in Figure 9.

Figure 9 PK-QT model and 90% CI (PK-ECG set, with NSAI as combination partner). Note: Blue symbols and curves represent data of early breast cancer patients; black symbols and curves represent data of advanced breast cancer patients; horizontal dotted lines are the reference lines at 30 ms and 60 ms.



2.3.5. Discussion on clinical pharmacology

The clinical pharmacology data in support of this application derived from study (CLEE011O12301C (NATALEE) and study A2207 (AMALEE) which were designed to investigate the efficacy and safety of ribociclib treatment in combination with an aromatase inhibitor for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence.

A population PK approach was conducted to characterize the pharmacokinetics of ribociclib.

The validation of the bioanalytical method for ribociclib and study sample analysis was adequate.

Since the increase in exposure was small in moderate and severe hepatic impairment subjects, no upfront dose adjustment is required in early breast cancer with the 400 mg starting dose if the patient has hepatic impairment. The text in SmPC section 4.2 have been updated to differentiate recommendations for early and metastatic breast cancer with regards to hepatic impairment.

The updated SmPC claims on drug-drug interactions are based on PBPK simulations with CYP3A4 inhibitors or inducers. The remaining parts of the information on interactions are adequate and remain unchanged in the SmPC.

The main update to the existing and accepted PBPK model is the use of an adapted healthy population to represent early cancer patients and a metastatic cancer patient population.

The modelling in the metastatic cancer population was part of variation II-41G and is not reassessed here in this procedure.

In the PBPK model, the early breast cancer population, was actually represented by the Simcyp healthy volunteer population file with a reduced coefficient of variance for the amount of microsomal protein per gram of liver and for the hepatic CYP3A4 abundance. For interaction claims, the mean or geometric mean is typically used, and variability is not considered to a large extent. Therefore, changes to the healthy

subject population file are not considered to have a substantial impact for the SmPC claims. The update of the healthy subjects population file for the already accepted PBPK model (at time of the initial MAA) is acceptable. The approved SmPC already contains text based on PBPK modelling in healthy subjects, thus the information from "early breast cancer" simulations is redundant and is not included in the SmPC.

The MAH initially did not propose upfront dose reduction in the case where a strong CYP3A4 inhibitor must be administered with ribociclib. Monitoring and if necessary, dose reduction were proposed instead. In study O12301C, patients receiving strong inhibitors (or inducers) of CYP3A4 were excluded from the study and strong inhibitors were on the list of prohibited medications. Thus, the proposed scenario with no upfront reduction has not been studied. A few patients did still receive strong inhibitors such as ketoconazole, ritonavir/lopinavir. The PBPK model predicts approximately a doubled exposure of ribociclib (400 mg) with a strong CYP3A4 inhibitor, in line with the interaction size being larger at lower ribociclib doses due to its autoinhibition. An upfront dose reduction from 400 mg to 200mg is thus in line with the predictions and it is reflected in the SmPC 4.2

For the moderate CYP3A4 inhibitor erythromycin, the geometric mean ratios of steady-state Cmax and AUC are predicted to be 1.13 and 1.23, respectively, for multiple dosing of 400 mg ribociclib with vs without coadministration of erythromycin, suggesting no apparent effect of moderate CYP3A4 inhibitors on ribociclib PK (see SmPC 4.5).

A moderate CYP3A4 inducer (efavirenz) may decrease steady-state ribociclib Cmax and AUC by 55% and 74%, respectively, at a ribociclib dose of 400 mg, and by 52% and 71%, respectively, at a ribociclib dose of 600 mg. This implies a risk of impaired efficacy, which is reflected in the SmPC.

Study O12301C is the main study with PK sampling in the target population (eBC). Since sparse PK sampling was used in the study, standard non-compartmental analysis (NCA) may not be applicable. The relative low number of samples collected per patient doesn't allow the complete characterization of the ribociclib PK profile, however, the PK of ribociclib was thoroughly characterized in aBC patients and healthy volunteers based on an analysis included in the initial MAA.

The presented PopPK approach represents a reduced model development scheme where only selected parameter(s) were re-estimated based on data from eBC patients. The number of parameters to re-estimate was kept to as few as possible, yet the developed model was to give acceptable description of the observed PK data from Study O12301C. Overall, this is considered a plausible strategy to describe PK in eBC patients by still re-using prior information from the previous PopPK model.

The Applicant did not provide a dedicated PopPK report. The previous PopPK model was used as a basis for characterizing the PK in eBC patients, in relation to aBC patients. Based on the provided pcVPC the updated PopPK model gives an acceptable description of the observed PK data in Study O12301C. Overall the updated model is considered acceptable where the re-estimated parameters were CL/F, IIV in absorption and changes to the residual error (going from a proportional model to an additive model). The inclusion of dose on CL explains the non-linear elimination processes that have not been mechanistically explained. A dose-dependency effect (17% higher CL/F) was identified at 400 vs 600 mg. The updated model is considered acceptable to support the general statement in SmPC 5.2 that a lower exposure is expected in eBC than in aBC patients administered with the same dosing regimen. However, due to limitations of the updated PopPK analysis, more detailed are not given in the SmPC. For instance, the implemented dose dependency is considered an empirical relationship which may even be confounded by additional unidentified factors affecting the PK properties of ribociclib. Furthermore, the sparse PK evidence collected in eBC patients is not sufficient for justifying the underlying factors involved in CL/F differences across indications.

The CL/F was found to be approximately 20% higher in eBC patients compared to aBC patients. This means that the exposure is expected to be lower in eBC patients than aBC patients administered the same dose regimen which is appropriately reflected in the SmPC 5.2.

For the PK-QTc analysis, the eBC data was pooled with the same dataset that was used to develop the previous PK-QTc model. This means that a fairly large database was used to develop the model (1372 patients) although only 117 were eBC patients from Study OC12301C which is a limitation. A standard workflow was used for developing the PK-QTc model which is acceptable in principle, however, the dataset used for model development is considered a critical limitation. Based on the provided documentation, Study OC12301C is not considered adequately designed for the purpose of performing a robust PK-QTc analysis. Apart from including a general statement from this analysis in SmPC section 5.1, the PK-QTc analysis is not considered acceptable for including specific model-based predictions in the SmPC for eBC patients.

QT prolongation was an important identified risk for ribociclib in the initial MAA where a concentration-dependency in QT prolongation was evident. The current analysis confirms that this trend exists also in eBC patients. Since eBC patients are treated with a lower ribociclib dose (400 mg vs 600 mg), a lower degree of QT prolongation is expected. The identification of eBC patients as a covariate on QT prolongation (indicating a lower QT prolongation of -5.37 ms even after accounting for a lower ribociclib dose in eBC patients) is questioned. This is a data-driven finding with unknown clinical relevance. Since the PK-QTc model had low impact, any model-based predictions which included this covariate effect is not included in the SmPC.

2.3.6. Conclusions on clinical pharmacology

The PK of ribociclib in early breast cancer patients is well characterised and supports the proposed posology.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Ribociclib is currently indicated in HR-positive, HER2-negative locally advanced or metastatic BC in combination with an Aromatase Inhibitor or fulvestrant, with a dose of 600 mg orally taken once daily for 21 consecutive days followed by seven days off treatment (one treatment cycle is 28 days).

In the current application the intended ribociclib dose is 400 mg orally taken once daily for 21 consecutive days followed by seven days off treatment, with a treatment duration of three years.

The 400 mg dose was selected based on consistent efficacy in post hoc exploratory analyses from the MONALEESA program, a potentially improved safety profile in terms of dose-dependent toxicities such as QTc prolongation and neutropenia as compared to the 600 mg starting dose, and supportive analyses including PK-QTcF and ANC exposure-response modelling, exposure-efficacy, and exploratory progression-free survival (PFS) analysis by dose reduction (See Pharmacology Section).

2.4.2. Main study

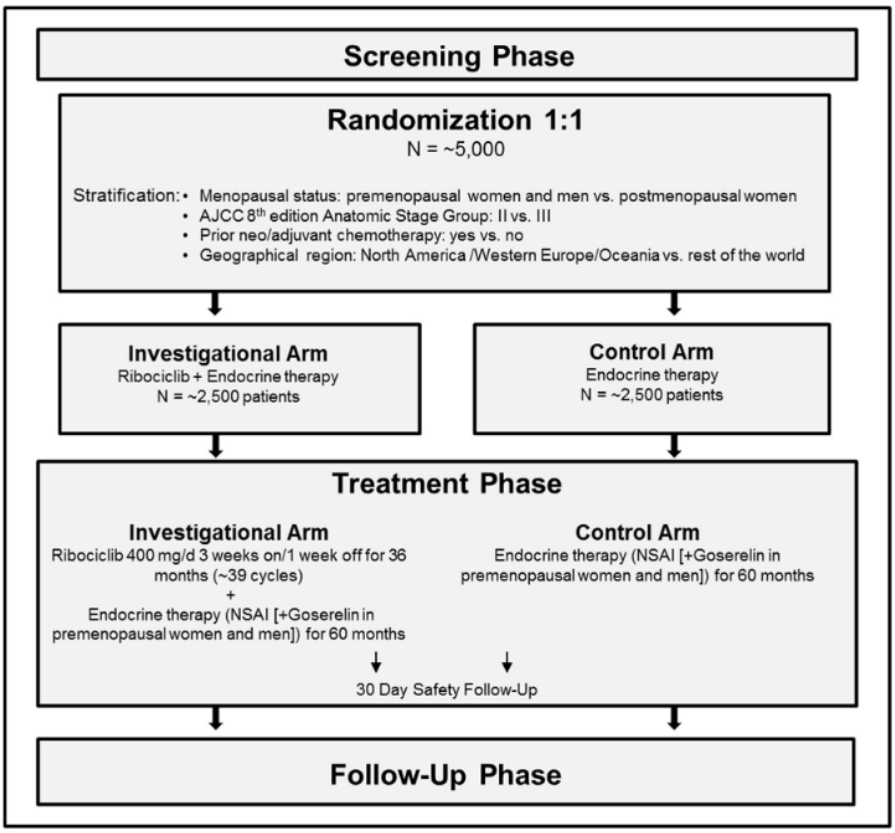
Study CLEE11O12301C -NATALEE

The pivotal study CLEE11O12301C, hereafter referred to as study O12301C, is a phase III, multicentre, randomised, open-label trial aiming at evaluating efficacy and safety of ribociclib with an Aromatase

Inhibitors (AI) vs. AI alone as adjuvant treatment in patients with HR-positive, HER2-negative early BC (eBC). For premenopausal women and for men goserelin was added to the treatment in accordance with current clinical guidelines.

In regard to description of the AI treatment in study O12301C, the abbreviation ET (endocrine therapy letrozole or anastrozole) is used throughout the assessment report.

Figure 10 Study design



Methods

Study participants

Selected key inclusion criteria

- Female and male patients ≥18 years of age (with known menopausal status if female)
- Histologically confirmed diagnosis of unilateral ER and/or PR-positive, HER2-negative invasive adenocarcinoma of the breast (patients with multicentric and/or multifocal tumours eligible if all tumours met the pathologic inclusion criteria)
- Stage II-III, regardless of nodal involvement
- For stage IIA without nodal involvement either
    - tumour grade 3 or
    - tumour grade 2 with high-risk genomic profile or Ki67 ≥20% has to be present
- Complete surgical resection with free tumour margins

- ECOG performance 0-1 and who were deemed eligible for adjuvant ET for at least a 60-month duration
- QTcF interval at screening <450 msec
- Neoadjuvant and/or adjuvant chemotherapy should be completed prior to screening
- Standard neoadjuvant and/or adjuvant ET before study enrolment was allowed, but randomisation should occur within 12 months of the initial start date of ET

Selected key exclusion criteria

- Prior CDK4/6 inhibitor treatment
- Prior tamoxifen, raloxifene, or AI treatment for risk reduction (`chemoprevention´) of BC
- Concurrent hormone replacement therapy
- Prior anthracycline treatment exceeding specified cumulative doses
- Distant metastases beyond regional lymph nodes (i.e., stage IV) or evidence of recurrence after curative surgery
- Clinically significant, uncontrolled heart disease and/or cardiac repolarisation abnormality (including among others Long QT syndrome and clinically significant cardiac arrythmias)

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 400 mg days 1-21 of each 28-day cycle plus ET (letrozole 2.5 mg daily or anastrozole 1mg daily) plus goserelin 3.6 mg subcutaneously of each 28-day cycle.
- Placebo plus ET (letrozole or anastrozole) plus goserelin.

Ribociclib and ET (letrozole or anastrozole) were administered orally together at approximately the same time each day with or without food.

Crossover between different types of ETs was not permitted in the study unless intolerable toxicity, patient request, or any other medically important event necessitated a change of ET. Goserelin was administered subcutaneously (premenopausal women and men only).

The scheduled ribociclib treatment duration was 36 months unless treatment was discontinued due to disease recurrence or unacceptable toxicity. ET treatment continued for at least 60 months from randomisation.

Mammography was planned at screening, every 12 months thereafter and as clinically indicated, until confirmation of distant recurrence (unless bilateral mastectomy was performed).

Additional radiologic examinations were planned at screening if clinically indicated and within four weeks of clinical suspicion of any recurrence or second primary non-breast invasive cancer.

Objectives

Outcomes/endpoints

Table 20 Objectives and related endpoints

Objective	Endpoint
Primary	
To compare iDFS for ribociclib + ET versus ET in patients with HR-positive, HER2-negative, eBC	iDFS using STEEP criteria, as assessed by Investigator
Secondary	
To evaluate the 2 treatment arms with respect RFS	RFS using STEEP criteria
To evaluate the 2 treatment arms with respect to DDFS	DDFS using STEEP criteria
To evaluate the 2 treatment arms with respect to OS	OS defined as time from date of randomization to date of death due to any cause
To evaluate PRO for health-related QoL in the 2 treatment arms	Change from baseline in the physical functioning sub-scale score and global health status / QoL scale score as assessed by EORTC QLQ-C30
To evaluate safety and tolerability of the treatment regimen	Frequency and severity of AEs, laboratory and ECG abnormalities
To characterize the PK of ribociclib when given in combination with NSAI (and goserelin if applicable)	PK parameters such as C_{trough} and other applicable parameters for ribociclib
Exploratory	
To explore the 2 treatment arms with respect to LRRFS	LRRFS defined as time from date of randomization to date of first event of local invasive breast recurrence, regional invasive recurrence, or death due to any cause
To explore use of subsequent anti-neoplastic therapy	Incidence of subsequent anti-neoplastic therapy and time to first subsequent anti-neoplastic therapy
To explore healthcare resource utilization	Number of patients hospitalized, total number of hospitalizations, and length of stay in hospitals, number of patients with Emergency Room and additional visits

The primary endpoint invasive disease-free survival (iDFS) was defined as the time from the date of randomisation to the date of the first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, contralateral invasive BC, a second primary non-breast invasive cancer (basal and squamous cell carcinomas of the skin excluded), or death due to any cause. iDFS events were to be assessed locally.

Secondary endpoints relapse-free survival (RFS), distant disease-free survival (DDFS), overall survival (OS), and the exploratory endpoint loco-regional recurrence-free survival (LRRFS) were defined as follows:

RFS – the time from date of randomisation to date of first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, or death due to any cause

DDFS – the time from date of randomisation to date of first event of distant recurrence, second primary non-breast invasive cancer (basal and squamous cell carcinomas of the skin excluded), or death due to any cause

OS – the time from randomisation to date of death due to any cause

LRRFS – the time from date of randomisation to date of first event of local invasive breast recurrence, regional invasive recurrence, or death due to any cause

All endpoints were investigator-assessed.

Analyses of the primary and secondary endpoints were based on the full analysis set (FAS). iDFS events were assessed locally and the analysis included all data observed up to the cut-off date. Objective confirmation using histological or cytological assessment was required to consider a recurrence an iDFS event. iDFS, RFS, and DDFS were assessed using the STandardised definitions for Efficacy EndPoints (STEEP criteria).

Sample size

This study was event driven. The assumptions made underlying the sample size estimation was based on the primary endpoint iDFS.

At the planning stage, the expected total sample size needed was approximately 4,000 subjects (randomized 1:1).

The enrolment of patients with Anatomic Stage II was to be capped at 40%.

After the study had started, changes were implemented which affected the assumptions initially made (CSP version 2.0 and CSP version 4.0).

The distribution of Anatomic Stage II and Stage III patients was amended, and it was decided to exclude Anatomic Stage II low risk patients. For patients with node-negative stage IIA tumours to be eligible, they had to be grade 3, or grade 2 with a high Ki67 index (≥20%) or considered high risk by a validated gene expression test (as defined in inclusion criterion #8).

Based on emergent external data, the total sample size was increased.

A third efficacy interim analysis was added.

Below is the sample size section as described in the latest protocol version (version 4.0) which added another 1,000 patients.

CSP version 4.0 (dated 27 August 2020)

The enrolment of patients was expected to be approximately 40% for the Anatomic Stage II (excluding low risk patients) and 60% for the Anatomic Stage III.

The 5-year iDFS rate for the patients with Anatomic Stage II (excluding low risk patients) was assumed to be approximately 79%.

The 5-year iDFS rate for the patients with Anatomic Stage III was assumed to be approximately 72%.

Given these assumptions, the overall 5-year iDFS of the control arm was assumed to be approximately 74.8%. It was further assumed that the comparison between ribociclib in addition to standard ET and standard ET alone was to result in a hazard ratio (HR) of 0.73.

The power calculation was based on a one-sided log-rank test at an overall 2.5% level of significance, a randomisation ratio of 1:1, and a 4-look group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function and a Lan-DeMets (O'Brien-Fleming) beta spending function to define a non-binding futility rule at the interim analyses, using an information fraction of 40% for the first interim analysis (futility only) and an information fraction of 70% and 85% for the second and third interim analyses (efficacy only), respectively.

A total of 500 iDFS events were then to provide a power of approximately 93% and 85% when the overall hazard ratio is 0.73 and 0.76, respectively.

Based on projected enrolment, a total of 5,000 patients were to be randomised to observe the targeted 500 iDFS events at about 44 months after the randomisation date of the first patient.

Table 21: Update of estimated timelines for interim and final analyses (CSP version 4.0).

	Months after randomisation of the first patient (approximation	iDFS events (information fraction)	Cumulative power against a hazard ratio of 0.73
Interim analysis 1	~~26~~ 27	~~150~~ 200 (40%)	0
Interim analysis 2	~~34~~ 35	~~263~~ 350 (70%)	~~54.6~~ 68.4%
Interim analysis 3	~~42~~ 39	~~375~~ 425 (85%)	84.8%
Final analysis	44	500	~~85.0~~ 93.1%

The final analysis will be performed after approximately 500 iDFS events have been documented.

Randomisation

Patients were to be assigned to one of the two treatment arms in a ratio of 1:1. Randomisation was to be stratified by the following factors:

- Menopausal status: premenopausal women and men vs. postmenopausal women
- AJCC 8th edition Anatomic Stage Group: Anatomic Stage Group II vs. Anatomic Stage Group III
- Prior neo-/adjuvant chemotherapy: yes vs. no
- Geographical region: North America/Western Europe/Oceania vs. rest of the world (RoW)

To account for the differences in the underlying recurrence rates in the early breast cancer population between the two Anatomic Stages, the number of patients with Anatomic Stage Group II was to be capped. Initially at approximately 40%, per CSP version 2.0 at approximately 50%.

Blinding (masking)

This is an open label study.

Statistical methods

The submitted SAP is version 3.0 (Amendment 2, dated 25 August 2022) and contains a version history. With SAP amendment 1 (SAP version 2.0, dated 26 July 2021) changes were implemented to align with CSP version 4.0, 27 August 2020). The first approved SAP version was dated 05 December 2018 which is before the first subject first visit.

The outcome submitted is from a third (added) interim analysis. This is to be considered the primary analysis of the primary endpoint.

Primary analysis set

The primary analysis was to be based on the Full Analysis Set (**FAS**). FAS was to include all randomised patients. Patients were to be analysed according to the randomised treatment arm and the strata they had been assigned to during the randomisation procedure.

Primary endpoint definition

The primary efficacy variable of the trial is **iDFS** (defined above).

The primary iDFS analysis was to include all data observed up-to the cut-off date.

Censoring pattern of iDFS

A summary of reasons for **iDFS censoring** has been provided by treatment arm.

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

1. Analysis cut-off date (censoring reason: 'Ongoing without event'),

2. Date of consent withdrawal (censoring reason: 'Withdrew consent'),

3. Date of Last Contact for patients lost to follow-up at EOT or Date of Visit/contact for patients lost to follow-up during follow-up phase (censoring reason: 'Lost to follow-up').

In addition, the time from iDFS censoring date to data cut-off date was to be summarized by time intervals in months: <3, 3 - < 6, 6 - < 12, 12 - < 18, 18 - <24 and by 12-month intervals thereafter if necessary. The gap time was calculated as ([analysis cut-off date] - [censoring date] + 1)/30.4375.

Recurrence documented after the initiation of new anti-neoplastic therapy was to be considered for the primary analysis provided recurrence assessments had continued after initiation of new cancer therapy.

Discontinuation due to clinical suspicion of recurrence without histological/cytological/imaging confirmation of recurrence was not to be considered as an iDFS event.

Primary endpoint analyses

The primary hypothesis was to be tested using a **stratified log-rank test** at an overall one-sided 2.5% level of significance accounting for the randomisation stratification factors: menopausal status, the AJCC 8th edition Anatomic Stage Group, prior neo-/adjuvant chemotherapy, and geographical region.

A **stratified Cox** regression was used to estimate the hazard ratio (HR) of iDFS along with a 95% confidence interval using the same strata information as the primary efficacy comparison. The iDFS survival distribution was estimated using the Kaplan-Meier method.

The primary efficacy variable was to be analysed at **three interim analyses** and a final analysis.

The first interim was to allow the trial to stop due to futility.

The second and third interim analyses were to allow the trial to declare superior efficacy.

The study had a group sequential design. iDFS was analysed using a Lan-DeMets (O'Brien-Fleming) alpha spending function and a non-binding Lan-DeMets (O'Brien-Fleming) beta spending function based on the data observed in the FAS up to the cut-off date, according to the treatment arm and strata assigned at randomisation.

Interim analyses

The statistical properties of the group sequential design are summarized in Table 22 below (CSP version 4.0, 27 August 2020).

Table 22 Simulated Probabilities to Stop for Efficacy or Futility at the Interim or Final iDFS Analysis

Scenario	Look	# iDFS events	Simulated cumulative probabilities (%)		Simulated incremental probabilities (%)	
			Stop for efficacy	Stop for futility	Stop for efficacy	Stop for futility
Under H_0 (HR=1)	Interim 1	200		32.7		32.7
	Interim 2	350	0.8		0.8	
	Interim 3	425	1.5	-	0.7	
	Final	500	2.3		0.8	
Under H_a (HR=0.73)	Interim 1	200		0.4		0.4
	Interim 2	350	68.4		68.4	
	Interim 3	425	84.8		16.3	
	Final	500	93.1		8.3	
Under other H_a (HR=0.76)	Interim 1	200		0.8		0.8
	Interim 2	350	54.0		54.0	
	Interim 3	425	73.3		19.3	
	Final	500	85.2		12.0	
Under other H_a (HR=0.80)	Interim 1	200		2.1		2.1
	Interim 2	350	35.3		35.3	
	Interim 3	425	53.5		18.2	
	Final	500	67.9		14.4	

Note: Simulation is performed in East 6.4 with number of simulations = 10,000 and randomization seed = 123

The results of the interim analyses were to be provided to the IDMC by the independent statistician who was not to be part of trial management.

The projected timing of interim and final analyses of iDFS is summarized in Table 21.

Supportive Analyses

As sensitivity analyses performed in the FAS, the hazard ratio and 95% CI for iDFS was to be obtained from:

- An unstratified and covariate unadjusted Cox model.
- A stratified and covariate adjusted Cox model. The covariates to be included will be detailed in the SAP.

iDFS was also to be analysed based on the PPS, using the same analysis conventions as in the primary efficacy analysis, if the FAS and PPS differ and if the primary analysis is significant.

In addition, the following supportive analyses were pre-defined:

• Number of patients and number of events by treatment arm within each stratum were to be presented along with the hazard ratio for treatment effect obtained using the Cox proportional hazards regression with corresponding confidence intervals, provided there was a sufficient number of events within the stratum. No p-values were to be presented for this analysis. Kaplan-Meier plots of survival distributions will be presented by stratum.

• Type of first iDFS event and site of the first iDFS event were to be reported.

• If there was any discrepancy between the strata classifications constructed using the eCRF data and those obtained from the IRT, a sensitivity analysis was to be performed in which a stratified Cox regression model were to be used to estimate the treatment hazard ratio and the associated 95% confidence interval based on the eCRF- derived strata. No other inferential statistics were to be provided.

• Timing of all recurrence assessments were to be depicted graphically by treatment arm in order to visually assess if the alignment with protocol schedule is similar across the arms.

Analysis of secondary efficacy endpoints

All secondary efficacy objectives were to be analysed at the primary analysis for iDFS (2nd or 3rd interim analyses if the efficacy boundary was crossed or final iDFS analysis) and at the time of end of trial. Each secondary efficacy endpoint was to be analysed in the FAS population according to the randomized treatment arm and strata assigned at randomisation.

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

Results

Participant flow

Figure 11 Participants' flow chart

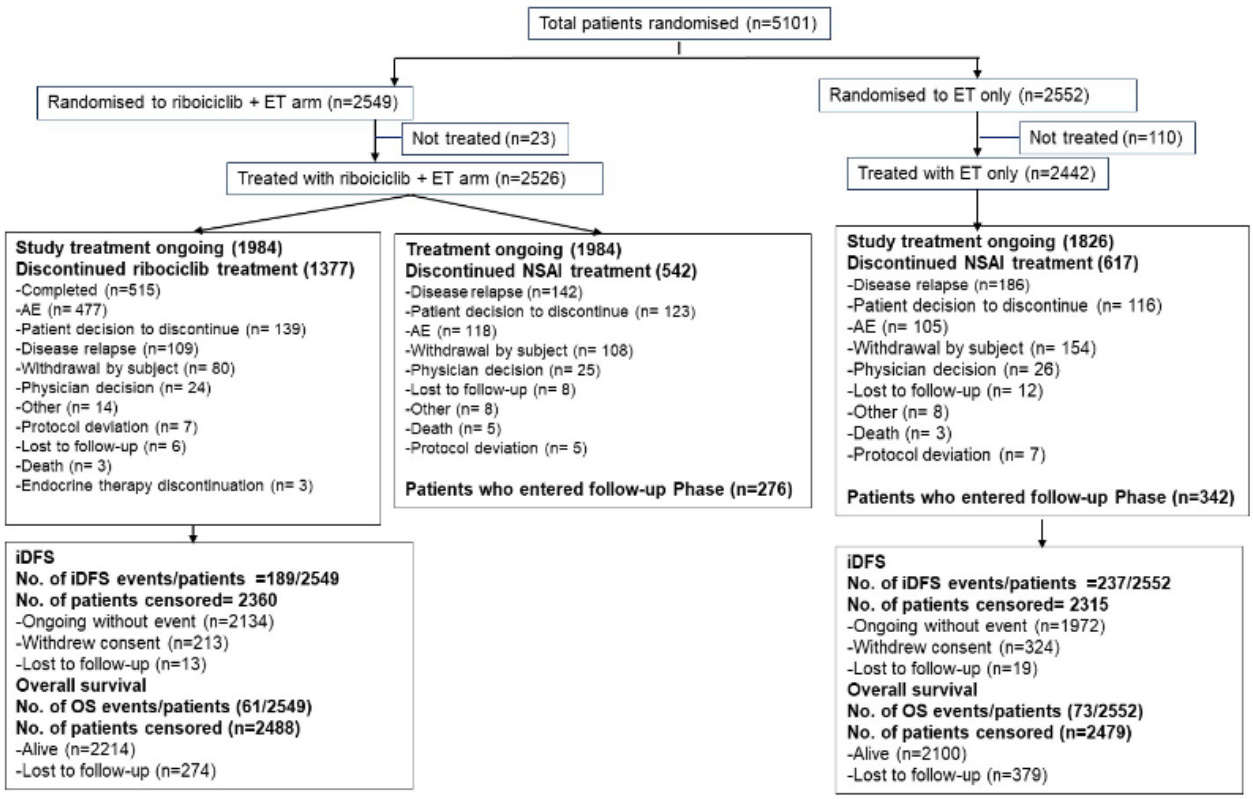


Table 23 Patient disposition by treatment arm, data at IA3 data cut-off (11 Jan 2023) (FAS)

Disposition/Reason	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Number of patients randomized	2549 (100)	2552 (100)	5101 (100)
Number of patients randomized but not treated	23 (0.9)	110 (4.3)	133 (2.6)
Number of patients treated with any treatment	2526 (99.1)	2442 (95.7)	4968 (97.4)
Number of patients who discontinued all treatment components	542 (21.3)	616 (24.1)	1158 (22.7)
Number of patients who discontinued ribociclib*	1377 (54.0)	0	1377 (27.0)
Number of patients who discontinued NSAI	542 (21.3)	617 (24.2)	1159 (22.7)
Number of patients still on treatment	1984 (77.8)	1826 (71.6)	3810 (74.7)
Primary reason for ribociclib discontinuation			
Adverse event	477 (18.7)	0	477 (9.4)
Completed	515 (20.2)	0	515 (10.1)
Death	3 (0.1)	0	3 (0.1)
Disease relapse	109 (4.3)	0	109 (2.1)
Endocrine therapy discontinuation	3 (0.1)	0	3 (0.1)
Lost to follow-up	6 (0.2)	0	6 (0.1)
Other	14 (0.5)	0	14 (0.3)
Patient decision to discontinue treatment	139 (5.5)	0	139 (2.7)
Physician decision	24 (0.9)	0	24 (0.5)
Protocol deviation	7 (0.3)	0	7 (0.1)
Withdrawal by subject	80 (3.1)	0	80 (1.6)
Number of patients who had their 30-day post-ribociclib safety follow-up visit	275 (10.8)	0	275 (5.4)
Primary reason for NSAI discontinuation			
Adverse event	118 (4.6)	105 (4.1)	223 (4.4)
Death	5 (0.2)	3 (0.1)	8 (0.2)
Disease relapse	142 (5.6)	186 (7.3)	328 (6.4)
Lost to follow-up	8 (0.3)	12 (0.5)	20 (0.4)
Other	8 (0.3)	8 (0.3)	16 (0.3)
Patient decision to discontinue treatment	123 (4.8)	116 (4.5)	239 (4.7)
Physician decision	25 (1.0)	26 (1.0)	51 (1.0)
Protocol deviation	5 (0.2)	7 (0.3)	12 (0.2)
Withdrawal by subject	108 (4.2)	154 (6.0)	262 (5.1)
Number of patients who had their 30-day post-NSAI safety follow-up visit	276 (10.8)	336 (13.2)	612 (12.0)
Number of patients who have entered the follow-up phase	276 (10.8)	342 (13.4)	618 (12.1)
Number of patients who discontinued from trial	333 (13.1)	451 (17.7)	784 (15.4)
Death	61 (2.4)	73 (2.9)	134 (2.6)
Lost to follow-up	18 (0.7)	24 (0.9)	42 (0.8)
Other	3 (0.1)	2 (0.1)	5 (0.1)
Physician decision	17 (0.7)	9 (0.4)	26 (0.5)
Pregnancy	1 (0.0)	0	1 (0.0)
Protocol deviation	4 (0.2)	5 (0.2)	9 (0.2)
Withdrawal by subject	229 (9.0)	338 (13.2)	567 (11.1)

*Includes patients who completed the 3-year treatment regimen

In total, 6,068 patients were screened, and 5,101 patients were included in study O12301C, of which 2,549 were randomised to the ribociclib + ET arm and 2,553 patients were randomised to the ET only arm.

At the data cut-off (DCO) of IA3 (11 Jan 2023), 133 the randomised patients had not received the allocated treatment (n=23 [0.9%] in the ribociclib + ET arm, and n=110 [4.3%] in the ET only arm, respectively).

Goserelin was administered for gonadal suppression in premenopausal women and in men. In total, 1,125 patients (44.1%) in the ribociclib + ET arm were premenopausal women and men (n=1,114 women, n=11 men), In the ET only arm, 1,128 patients (44.2%) were premenopausal women and men (n=1,119 women, n=9 men). Goserelin treatment was received by 1,101 patients (43.2%) in the ribociclib + ET arm and 1,066 patients (41.8%) in the ET only arm. Of the patients who were treated with goserelin, 24.7% in the ribociclib + ET arm and 30.1% in the ET only arm had discontinued goserelin treatment as

of the DCO of IA3. Disease relapse as the reason for goserelin discontinuation was reported for 4.4% of patients in the ribociclib + ET arm and 6.1% of patients in the ET only arm, respectively.

Stratification according to menopausal status (premenopausal women, and men vs. postmenopausal women), AJCC 8th edition Stage (stage II vs. stage III), prior neoadjuvant/adjuvant chemotherapy (yes vs. no), and geographical region (North America/Western Europe/Oceania vs. rest of the world) was incorporated in the randomisation design. There was high concordance between the stratum recorded at the time of randomisation and the actual stratum recorded in the clinical database through the data collected on eCRF and hence, the rate of mis-randomisation due to wrong stratification factors was low.

Recruitment

Study period

Study initiation date: 7 Dec 2018

Data cut-off date, primary analysis: 11 Jan 2023

Data cut-off date, final iDFS analysis: 21 Jul 2023

Study O12301 is still ongoing.

Study centres

The study was conducted at 393 sites in the following 20 countries: Argentina (1), Australia (2), Austria (3), Belgium (4), Brazil (5), Canada (6), China (7), France (8), Germany (9), Hungary (10), Ireland (11), Italy (12), Republic of Korea (13), Poland (14), Rumania (15), Russia (16), Spain (17), Taiwan (18), United Kingdom (19), and United States (20).

Conduct of the study

The original study protocol is dated 27 Aug 2018. The protocol has been amended five times, of which two were local amendments for Germany and the USA, respectively. The current protocol version is version 4.0, dated 27 Aug 2020.

Selected key features of amendments are summarised below:

Version 2.0, 20 Jun 2019

- A clarification of which concomitant medications that were allowed vs. not allowed was added.
- A capping rule amendment was included to allow for a better representation of stage II and III patients (50% each).
- After consultation with the EMA, it was decided to include stage II patients with higher risk of recurrence compared to protocol version 1.0. Therefore, the iDFS event rate was expected to increase and therefore the power for the iDFS endpoint was increased from 80% to 85%.

Update of estimated timelines for interim and final analyses

	Months after randomisation of the first patient (approximation	iDFS events (information fraction)	Cumulative power against a hazard ratio of 0.73
Interim analysis 1	26	133 150 (40%)	0

Interim analysis 2	34	232 263 (70%)	47.6 54.6%
Final analysis	42	332 375	80.0 85.0%

- Clarification that if the primary efficacy analysis is statistically significant, additional descriptive analyses of iDFS will also be performed approximately two years after the primary iDFS analysis and at end of trial. Consequently, addition of additional OS analysis to coincide with the additional iDFS analysis.

Version 3.0, 23 Jan 2020

- Concurrent use of hormone replacement therapy was stated explicitly as an exclusion criterion.
- Wording added to provide clear guidance on the management of interstitial lung disease (ILD)/pneumonitis and dose adjustment of ribociclib for ILD/pneumonitis.

Version 4.0, 27 Aug 2020

- Update made to describe emerging data from other CDK4/6 inhibitor trials indicating a potential greater treatment benefit in stage III patients. Consequently, the sample size was increased to include more stage III patients. The number of stage II patients will be capped at approximately 2,000, out of a total study population of approximately 5,000 patients.
- Update of interim and final analyses due to the increased sample size and update of selected statistical methods. Interim analysis (IA) 1 is a futility analysis, whereas IAs 2 and 3 are intended to declare superior efficacy of the experimental arm.

Protocol deviations

At least one protocol deviation was reported for 70.2% of the patients. The percentage of patients with deviations was slightly higher in the ribociclib + ET arm compared to that in the ET only arm (73.3% vs. 67.1%). A total of 47 patients (0.9%) were excluded from the per protocol set (PPS) due to major deviations. Forty-six patients (0.9%) were excluded from the PPS due to inclusion/exclusion criteria not being met (n=26 due to not meeting the stage requirement, n=18 due to unavailable HER2 status, and n=2 due to having metastatic disease at study entry). One patient (<0.1%) was excluded from the PPS due to being given a different treatment than originally randomised to; this patient was randomised to the ET only arm but was administered two days of ribociclib treatment (dispensing error) after which ribociclib was recalled and the patient resumed treatment with ET only.

In total, 2,460 patients (48.2%) reported at least one study assessment and procedure protocol deviation and 1,157 patients (22.7%) reported at least one inclusion/exclusion protocol deviation. The most commonly reported study assessment and procedure protocol deviation was mammography not regularly assessed as per protocol (1,062 patients, 20.8%). The most commonly reported inclusion/exclusion protocol deviation was baseline laboratory results criteria (blood salts, i.e., potassium, calcium and magnesium) not met (218 patients, 4.3%).

Table 24 Protocol deviations (FAS)

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

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

In total, protocol deviations due to the COVID-19 pandemic were reported in 1,016 patients (19.9%). The number of patients with deviations due to the COVID-19 pandemic was lower in the ribociclib + ET arm compared to that in the ET only arm (16.6% vs. 23.2%). Overall, the most reported protocol deviations due to the COVID-19 pandemic were due to planned visits not done at sites (641 patients, 12.6%) followed by missing visits (377 patients, 7.4%). Protocol deviations due to the COVID-19 pandemic such as changes in drug supply method, treatment not given, patient discontinuation due to COVID-19 situation, and changes in procedures due to COVID-19 were each reported in less than 4.0% of patients.

Baseline data

Table 25 Demographic characteristics (FAS)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Age group			
<45	611 (24.0)	591 (23.2)	1202 (23.6)
45 to 54	849 (33.3)	895 (35.1)	1744 (34.2)
55 to 64	682 (26.8)	700 (27.4)	1382 (27.1)
>=65	407 (16.0)	366 (14.3)	773 (15.2)
Age (years)			
n	2549	2552	5101
Mean	52.9	52.7	52.8
SD	10.75	10.77	10.76
Min	24	24	24
Median	52.0	52.0	52.0
Max	90	89	90
Gender			
Male	11 (0.4)	9 (0.4)	20 (0.4)
Female	2538 (99.6)	2543 (99.6)	5081 (99.6)
Race			
White	1876 (73.6)	1868 (73.2)	3744 (73.4)
Black or African American	42 (1.6)	47 (1.8)	89 (1.7)
Asian	341 (13.4)	334 (13.1)	675 (13.2)
Native Hawaiian or Other Pacific Islander	3 (0.1)	1 (0.0)	4 (0.1)
American Indian or Alaska Native	4 (0.2)	3 (0.1)	7 (0.1)
Other	145 (5.7)	172 (6.7)	317 (6.2)
Missing	138 (5.4)	127 (5.0)	265 (5.2)
Ethnicity			
Hispanic or Latino	212 (8.3)	223 (8.7)	435 (8.5)
Not Hispanic or Latino	2076 (81.4)	2054 (80.5)	4130 (81.0)
Unknown	172 (6.7)	201 (7.9)	373 (7.3)
Missing	89 (3.5)	74 (2.9)	163 (3.2)
Region			
Asia	281 (11.0)	290 (11.4)	571 (11.2)
Europe	1505 (59.0)	1506 (59.0)	3011 (59.0)
North America/Australia	624 (24.5)	612 (24.0)	1236 (24.2)
Latin America	139 (5.5)	144 (5.6)	283 (5.5)
ECOG performance status			
0	2106 (82.6)	2132 (83.5)	4238 (83.1)
1	440 (17.3)	418 (16.4)	858 (16.8)
Missing	3 (0.1)	2 (0.1)	5 (0.1)
Weight (kg)			
n	2534	2542	5076
Mean	72.4	72.2	72.3
SD	16.20	15.53	15.86
Min	38	41	38
Median	70.0	70.0	70.0
Max	166	169	169
Height (cm)			
n	2523	2522	5045
Mean	162.9	162.7	162.8
SD	6.78	6.85	6.81
Min	140	140	140
Median	163.0	163.0	163.0
Max	198	191	198
BMI (kg/m²)			
n	2518	2521	5039
Mean	27.3	27.3	27.3
SD	5.81	5.70	5.76
Min	16	15	15
Median	26.3	26.5	26.4
Max	56	59	59

Weight and height are the last non-missing assessments on or before the date of randomization.
BMI: body mass index is calculated based on raw data measurements.

Table 26 Disease characteristics (FAS)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Tumor Location			
Right	1277 (50.1)	1258 (49.3)	2535 (49.7)
Left	1271 (49.9)	1287 (50.4)	2558 (50.1)
Bilateral	1 (0.0)	7 (0.3)	8 (0.2)
Missing	0	0	0
Histopathological grade at diagnosis - n (%)			
GX	30 (1.2)	32 (1.3)	62 (1.2)
G1	218 (8.6)	240 (9.4)	458 (9.0)
G2	1458 (57.2)	1451 (56.9)	2909 (57.0)
G3	521 (20.4)	549 (21.5)	1070 (21.0)
Not Done	292 (11.5)	258 (10.1)	550 (10.8)
Missing	30 (1.2)	22 (0.9)	52 (1.0)
T stage at diagnosis - n (%)			
TX	175 (6.9)	173 (6.8)	348 (6.8)
T0	4 (0.2)	7 (0.3)	11 (0.2)
Tis	2 (0.1)	3 (0.1)	5 (0.1)
T1	471 (18.5)	442 (17.3)	913 (17.9)
T2	1181 (46.3)	1235 (48.4)	2416 (47.4)
T3	471 (18.5)	472 (18.5)	943 (18.5)
T4	200 (7.8)	184 (7.2)	384 (7.5)
Missing	45 (1.8)	36 (1.4)	81 (1.6)
N stage at diagnosis - n (%)			
NX	272 (10.7)	264 (10.3)	536 (10.5)
N0	694 (27.2)	737 (28.9)	1431 (28.1)
N1	1050 (41.2)	1049 (41.1)	2099 (41.1)
N2	332 (13.0)	292 (11.4)	624 (12.2)
N3	151 (5.9)	175 (6.9)	326 (6.4)
Missing	50 (2.0)	35 (1.4)	85 (1.7)
Ki67 score at initial diagnosis			
n	1861	1908	3769
Mean	27.1	27.1	27.1
SD	19.88	19.50	19.69
Min	0	0	0
Median	20.0	20.5	20.0
Max	99	100	100
Ki67 category at initial diagnosis			
<=14%	508 (19.9)	508 (19.9)	1016 (19.9)
>14%	1353 (53.1)	1400 (54.9)	2753 (54.0)
<=20%	938 (36.8)	954 (37.4)	1892 (37.1)
>20%	923 (36.2)	954 (37.4)	1877 (36.8)
Missing	688 (27.0)	644 (25.2)	1332 (26.1)
Histopathological grade on surgical specimen - n (%)			
GX	32 (1.3)	30 (1.2)	62 (1.2)
G1	213 (8.4)	217 (8.5)	430 (8.4)
G2	1460 (57.3)	1432 (56.1)	2892 (56.7)
G3	684 (26.8)	702 (27.5)	1386 (27.2)
Not Done	159 (6.2)	168 (6.6)	327 (6.4)
Missing	1 (0.0)	3 (0.1)	4 (0.1)
T stage on surgical specimen - n (%)			
TX	20 (0.8)	9 (0.4)	29 (0.6)
T0	56 (2.2)	52 (2.0)	108 (2.1)
Tis	16 (0.6)	19 (0.7)	35 (0.7)
T1	774 (30.4)	761 (29.8)	1535 (30.1)
T2	1162 (45.6)	1198 (46.9)	2360 (46.3)
T3	427 (16.8)	422 (16.5)	849 (16.6)
T4	92 (3.6)	91 (3.6)	183 (3.6)
Missing	2 (0.1)	0	2 (0.0)
N stage on surgical specimen - n (%)			
NX	2 (0.1)	5 (0.2)	7 (0.1)
N0	378 (14.8)	418 (16.4)	796 (15.6)
N1	1062 (41.7)	1039 (40.7)	2101 (41.2)
N2	733 (28.8)	690 (27.0)	1423 (27.9)
N3	372 (14.6)	399 (15.6)	771 (15.1)
Missing	2 (0.1)	1 (0.0)	3 (0.1)
Ki67 score on surgical specimen [1]			
n	1269	1332	2601
Mean	20.6	20.9	20.7
SD	17.82	18.15	17.99
Min	0	0	0
Median	15.0	15.0	15.0
Max	99	98	99

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Ki67 category on surgical specimen			
<=14%	541 (21.2)	577 (22.6)	1118 (21.9)
>14%	728 (28.6)	755 (29.6)	1483 (29.1)
<=20%	817 (32.1)	864 (33.9)	1681 (33.0)
>20%	452 (17.7)	468 (18.3)	920 (18.0)
Missing	1280 (50.2)	1220 (47.8)	2500 (49.0)
Time since initial diagnosis (months)			
n	2517	2528	5045
Mean	11.8	11.8	11.8
SD	3.53	3.58	3.55
Min	1	1	1
Median	11.7	11.7	11.7
Max	23	27	27
Predominant histology - n (%)			
Invasive ductal carcinoma NOS	1857 (72.9)	1881 (73.7)	3738 (73.3)
Invasive lobular	455 (17.9)	450 (17.6)	905 (17.7)
Carcinoma medullary	1 (0.0)	1 (0.0)	2 (0.0)
Mucinous	17 (0.7)	16 (0.6)	33 (0.6)
Papillary	18 (0.7)	12 (0.5)	30 (0.6)
Tubular	5 (0.2)	3 (0.1)	8 (0.2)
Ductal Carcinoma In Situ	1 (0.0)	0	1 (0.0)
Lobular Carcinoma In Situ	0	0	0
Other	194 (7.6)	189 (7.4)	383 (7.5)
Missing	1 (0.0)	0	1 (0.0)
Prior surgery - n (%)			
Mastectomy	1664 (65.3)	1691 (66.3)	3355 (65.8)
Breast conserving surgery	978 (38.4)	963 (37.7)	1941 (38.1)
Axillary lymph node dissection	2165 (84.9)	2149 (84.2)	4314 (84.6)
Sentinel lymph node biopsy	926 (36.3)	920 (36.1)	1846 (36.2)
Other	143 (5.6)	162 (6.3)	305 (6.0)
Missing	0	0	0
HER2 ISH result prior to surgery (reported only if performed) - n (%)			
Amplification	4 (0.2)	7 (0.3)	11 (0.2)
Non-Amplification	612 (24.0)	653 (25.6)	1265 (24.8)
Equivocal	19 (0.7)	13 (0.5)	32 (0.6)
Unknown	6 (0.2)	11 (0.4)	17 (0.3)
HER2 ISH result from the surgical specimen (reported only if performed) - n (%)			
Amplification	2 (0.1)	1 (0.0)	3 (0.1)
Non-Amplification	417 (16.4)	423 (16.6)	840 (16.5)
Equivocal	1 (0.0)	1 (0.0)	2 (0.0)
Unknown	2 (0.1)	2 (0.1)	4 (0.1)
HER2 IHC score prior to surgery (reported only if performed) - n (%)			
0	856 (33.6)	881 (34.5)	1737 (34.1)
1+	862 (33.8)	813 (31.9)	1675 (32.8)
2+	464 (18.2)	480 (18.8)	944 (18.5)
3+	5 (0.2)	5 (0.2)	10 (0.2)
Unknown	21 (0.8)	21 (0.8)	42 (0.8)
HER2 IHC score from the surgical specimen (reported only if performed) - n (%)			
0	625 (24.5)	610 (23.9)	1235 (24.2)
1+	513 (20.1)	516 (20.2)	1029 (20.2)
2+	235 (9.2)	262 (10.3)	497 (9.7)
3+	1 (0.0)	3 (0.1)	4 (0.1)
Unknown	6 (0.2)	10 (0.4)	16 (0.3)
ER/PR combination statuses - n (%)			
ER+/PR+	2172 (85.2)	2132 (83.5)	4304 (84.4)
ER+/PR-	359 (14.1)	392 (15.4)	751 (14.7)
ER-/PR+	3 (0.1)	12 (0.5)	15 (0.3)
ER+/UNK	10 (0.4)	13 (0.5)	23 (0.5)
UNK/PR+	2 (0.1)	2 (0.1)	4 (0.1)
UNK/PR-	1 (0.0)	1 (0.0)	2 (0.0)
UNK/UNK	2 (0.1)	0	2 (0.0)
AJCC 8th ed. anatomic stage - n (%)			
Stage 0	0	0	0
Stage I	9 (0.4)	5 (0.2)	14 (0.3)
Stage II	1011 (39.7)	1034 (40.5)	2045 (40.1)
Stage III	1528 (59.9)	1512 (59.2)	3040 (59.6)
Stage IV	0	0	0
Missing	1 (0.0)	1 (0.0)	2 (0.0)
Genomic test			
Endopredict	23 (0.9)	28 (1.1)	51 (1.0)
Mammaprint	46 (1.8)	51 (2.0)	97 (1.9)
Oncotype DX	120 (4.7)	129 (5.1)	249 (4.9)
Pam50	38 (1.5)	29 (1.1)	67 (1.3)
Other	109 (4.3)	103 (4.0)	212 (4.2)

Characteristic	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
N status for subgroup analysis used in AJCC Stage derivation [2]			
N0	285 (11.2)	328 (12.9)	613 (12.0)
N1-N3	2261 (88.7)	2219 (87.0)	4480 (87.8)
>N3	0	0	0
Missing	3 (0.1)	5 (0.2)	8 (0.2)

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

Baseline data

Prior and concomitant therapy

Overall, 44.6% and 84.5% of patients had received prior antineoplastic medications in the neoadjuvant and adjuvant settings, respectively, prior to study entry. In total, 2,249 patients (88.2%) in the ribociclib + ET arm and 2,245 patients (88.0%) in the ET only arm had received prior chemotherapy, of which taxanes were the most common (84.2% of the patients in the ribociclib + ET arm and 83.5% in the ET only arm). Per protocol, patients were allowed to initiate adjuvant ET up to 12 months before randomisation and a total of 1,824 patients (71.6%) in the ribociclib + ET arm and 1,801 patients (70.6%) in the ET only arm had received prior ET. AIs were the most common prior ET in both treatment arms (62.8% in the ribociclib + ET arm, 62.4% in the ET only arm). The median duration of prior ET was 2.8 months (range 0-16) in the ribociclib + ET arm and 2.9 months (range 0-54) in the ET only arm.

Prior radiotherapy due to breast cancer was received by 2,292 patients (89.9%) in the ribociclib + ET arm and by 2,302 patients (90.2%) in the ET only arm. The median time since end of last radiotherapy was 2.3 months (range 0-14) in both treatment arms. All but one patient in the ribociclib + ET arm and all patients in the ET only arm had received prior breast cancer surgery with a median time since last surgery 7.9 months (range 0-18) in the ribociclib + ET arm and 7.8 months (range 0-21) in the ET only arm.

Numbers analysed

Table 27 Analysis set (all randomised patients)

Analysis set	Ribociclib + ET N=2549 n (%)	ET only N=2552 n (%)	Total N=5101 n (%)
Full analysis set	2549 (100)	2552 (100)	5101 (100)
Safety analysis set	2524 (99.0)	2444 (95.8)	4968 (97.4)
Per-protocol set	2496 (97.9)	2424 (95.0)	4920 (96.5)
Pharmacokinetic analysis set	108 (4.2)	0	108 (2.1)

Note: Denominator for percentages is based on the number of patients in the Full analysis set.

In total, 5,101 patients were randomised 1:1 to the two treatment arms between 10 Jan 2019 and 20 April 2021 and constituted the full analysis set (FAS), which was used for efficacy analyses.

All patients who received at least one dose of ribociclib or ET were included in the safety analysis set, which in total comprised 97.4% of all patients. All patients who received at least one dose of ribociclib and had at least on evaluable post-dose concentration measurement were included in the pharmacokinetic analysis set.

Furthermore, the patients in the FAS who were compliant with requirements of the protocol (i.e., received study treatment and were not excluded due to major protocol deviations) were included in the per protocol set (PPS). In total, 133 patients who did not receive any treatment, 47 patients with major protocol deviations, and one patient who by mistake received the wrong study treatment (ET only instead of ribociclib + ET) and withdrew consent for the study were excluded from the PPS. In the study protocol it is stated that sensitivity analyses of the primary endpoint iDFS may be performed using data from the PPS if the FAS and PPS differ and if the primary analysis is significant.

Outcomes and estimation

Primary endpoint iDFS

The primary analysis is based on data from the IA3 as of DCO 11 Jan 2023, with 426 iDFS events and median follow-up 27.7 months (range 0-45 months). Of the 426 investigator-assessed iDFS events, seven did not have a protocol-specified method of validation to support the event and were documented as protocol deviations.

At DCO for IA3, 515 (20.2%) patients in the ribociclib + ET arm had completed the full 36 months of ribociclib treatment, and 1,449 patients (57.4%) had completed 24 months of ribociclib treatment. Based on the third interim analysis, it is estimated that the maximum possible number of patients to complete 3-year treatment with ribociclib plus ET will be approximately 75.0%.

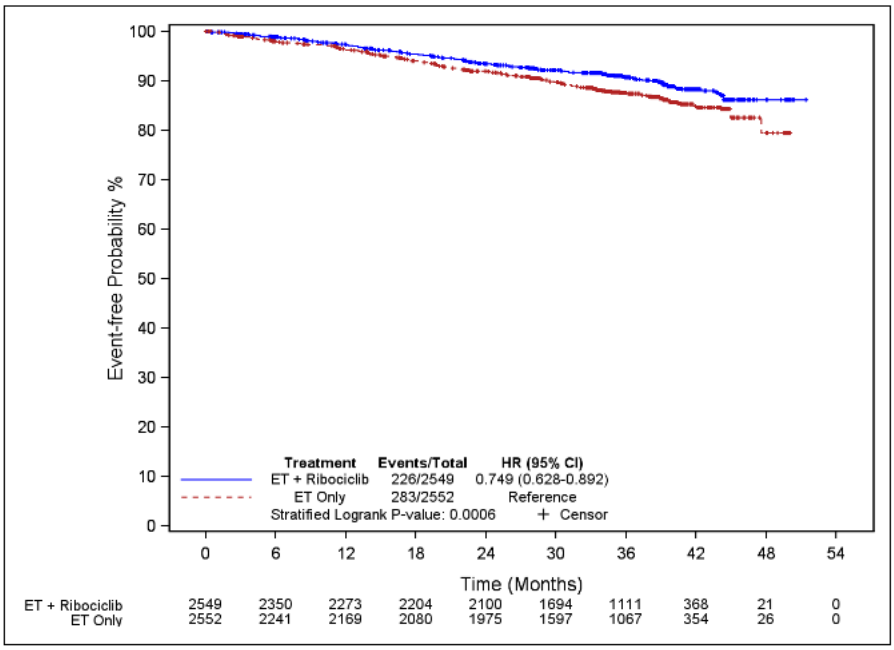
The hazard ratio (HR) of the primary endpoint iDFS was 0.748 (95% confidence interval [CI] 0.618, 0.906, 1-sided p-value=0.0014) in favour of the ribociclib + ET arm. The median time to iDFS was not reached (NR) in any of the treatment arms but in general, the iDFS event-free probability remained higher in the ribociclib + ET arm.

The 3-year iDFS rates were 90.4% (95% CI 88.6, 91.9) in the ribociclib + ET arm and 87.1% (95% CI 85.3, 88.8) in the ET only arm, reflecting a 3.3% absolute benefit favouring ribociclib + ET.

Final iDFS data as of DCO 21 Jul 2023 were consistent with the primary analysis with HR=0.749 (95% CI 0.628, 0.892, 1-sided p-value 0.0006). The median time to iDFS was NR in both treatment arms. At the final analysis, a total of 509 iDFS events had occurred (n=226 in the ribociclib + ET arm vs. n=283 in the ET only arm, respectively). The median follow-up at final iDFS analysis was 33.3 months (range 0-51 months), 6.3 months longer compared to at IA3.

At the final iDFS analysis (DCO 21 Jul 2023), an additional 576 patients had completed the full 3-year ribociclib treatment duration since the IA3 analysis. In total, 1,996 (78.3%) patients in the ribociclib + ET arm had then discontinued ribociclib; 1,091 (42.8%) of the patients had completed the 3-year ribociclib treatment, 498 (19.5%) discontinued due to AEs, 135 (5.3%) due to patient decision to discontinue, and 122 (4.8%) due to disease recurrence.

Figure 12 *Kaplan-Meier plot for iDFS (final iDFS analysis, 21 Jul 2023 data cut-off) (FAS)*



p-value from stratified log-rank test is one-sided.

Table 28 Kaplan-Meier estimates for iDFS (final iDFS analysis, 21 Jul 2023 data cut-off) (FAS)

ET + ribociclib N=2549		ET only N=2552	
Time	KM % estimate 95% CI	Time	KM % estimate 95% CI
Month 6	98.9 (98.4, 99.2)	Month 6	97.9 (97.3, 98.4)
Month 12	97.3 (96.5, 97.9)	Month 12	96.3 (95.4, 97.0)
Month 18	95.4 (94.5, 96.2)	Month 18	94.0 (93.0, 94.9)
Month 24	93.5 (92.4, 94.4)	Month 24	92.0 (90.8, 93.0)
Month 30	92.1 (90.9, 93.1)	Month 30	89.7 (88.3, 90.9)
Month 36	90.7 (89.3, 91.8)	Month 36	87.6 (86.1, 88.9)
Month 42	88.3 (86.4, 89.9)	Month 42	84.8 (82.8, 86.6)
Month 48	86.2 (83.5, 88.5)	Month 48	79.5 (71.4, 85.5)
Month 54	NE (NE, NE)	Month 54	NE (NE, NE)

NE = Not estimable.
n: the number of events
m: the number of patients censored

As shown in the table above, the 3-year iDFS rates at DCO for final iDFS analysis were 90.7% (95% CI 89.3, 91.8) in the ribociclib + ET arm and 87.6% (95% CI 86.1, 88.9) in the ET only arm, reflecting a 3.1% absolute benefit favouring ribociclib + ET.

Key baseline factors included age, ER/PR status, and ET type.

Table 29 Cox regression model for iDFS stratified by randomisation factors and adjusted for key baseline and prognostic factors (final iDFS analysis 21 Jul 2023 data cut-off) (FAS)

Treatment	Covariate	Level of Covariate	Comparison	Hazard Ratio	95% CI
ET + ribociclib			vs. ET only	0.752	(0.631, 0.897)
ET only					
	Age	< 45 years old	vs. >= 65 years old	0.755	(0.521, 1.095)
		45 - 54 years old	vs. >= 65 years old	0.697	(0.513, 0.947)
		55 - 64 years old	vs. >= 65 years old	0.855	(0.663, 1.104)
		>= 65 years old			
	ER/PR status	ER+PR+	vs. other	0.563	(0.459, 0.692)
		Other			
	ET type	Letrozole	vs. Anastrozole	0.906	(0.753, 1.092)
		Anastrozole			

The stratification factors in each model are premenopausal women and men vs. postmenopausal women, anatomic stage group II vs. anatomic stage group III, prior neo-/adjuvant chemotherapy (yes vs. no) and North America/Western Europe/Oceania vs. rest of world.

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Program: T_iDFS_COX_ADJ.sas Page 1 of 1

The most common type of first IDFS event in both treatment arms was distant recurrence. In total, 4.7% distance recurrence iDFS events were reported in the ribociclib + ET arm compared to 6.7% in the ET only arm.

Table 30 Type and site of first iDFS event (final iDFS analysis 21 Jul 2023 data cut-off) (FAS)

	ET+Ribociclib N=2549	ET Only N=2552
Type of first iDFS event		
Invasive ipsilateral breast tumor recurrence	8 (0.31%)	8 (0.31%)
Local/regional invasive recurrence	23 (0.90%)	40 (1.57%)
Distant recurrence	146 (5.73%)	205 (8.03%)
Invasive contralateral breast cancer	9 (0.35%)	9 (0.35%)
Death	17 (0.67%)	7 (0.27%)
Primary cause of death adverse event	15 (0.59%)	3 (0.12%)
Primary cause of death disease recurrence/progression	1 (0.04%)	-
Primary cause of death other	1 (0.04%)	4 (0.16%)
Second primary non-breast invasive cancer	34 (1.33%)	34 (1.33%)
Site(s) of iDFS event recurrence (excluding death and second primary non-breast invasive cancer)		
Ipsilateral breast	8 (0.31%)	8 (0.31%)
Ipsilateral chest wall/skin	11 (0.43%)	15 (0.59%)
Ipsilateral axilla	5 (0.20%)	8 (0.31%)
Regional lymph nodes	10 (0.39%)	21 (0.82%)
Contralateral breast (with or without contralateral lymph nodes)	9 (0.35%)	9 (0.35%)
Bone	87 (3.41%)	112 (4.39%)
Liver	43 (1.69%)	67 (2.63%)
Lung/pleura	29 (1.14%)	47 (1.84%)
Central nervous system	14 (0.55%)	18 (0.71%)
Distant lymph nodes	23 (0.90%)	30 (1.18%)
Other	10 (0.39%)	13 (0.51%)

-Patients may have multiple iDFS recurrence sites counted in the table, but are only counted once per patient per site.

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Program Name: T_iDFS_TYPE_SITE.sas Page 1 of 1

At DCO for the final analysis, the total proportion of patients censored for iDFS was comparable between the ribociclib plus ET arm and the ET only arm (91.1% vs. 88.9%). The predominant censoring reason in both treatment arms was `ongoing without event´.

Table 31 iDFS censoring by treatment arm (final iDFS analysis, 21 Jul 2023 data cut-off) (FAS)

	Number of patients N=5101 n (%)
Ribociclib + ET (N=2549)	
Number of patients with iDFS event	226 (8.9)
Number of patients censored	2323 (91.1)
Reason for censoring	
Ongoing without event	2073 (81.3)
Withdrew consent	233 (9.1)
Lost to follow-up	17 (0.7)
ET only (N=2552)	
Number of patients with iDFS event	283 (11.1)
Number of patients censored	2269 (88.9)
Reason for censoring	
Ongoing without event	1901 (74.5)
Withdrew consent	343 (13.4)
Lost to follow-up	25 (1.0)

Secondary endpoints

Relapse-free survival (RFS)

As of DCO for the final iDFS analysis, HR for the secondary endpoint **RFS** was 0.727 (95% CI 0.602, 0.887, nominal 1-sided p-value=0.0004) in favour of the ribociclib + ET arm. At DCO for the final iDFS analysis, 7.5% (192/2549) of the patients in the ribociclib + ET arm and 9.7% (248/2552) of the patients in the ET only arm had had an RFS event. The estimated 3-year RFS rates were 92.1% (95% CI 90.9, 93.2) in the ribociclib + ET arm and 89.1% (95% CI 87.6, 90.4) in the ET only arm, translating into an absolute risk reduction of 3.0% in favour of ribociclib + ET treatment. This is in line with the primary analysis. The proportion of patients censored for RFS was comparable between the two treatment arms (92.5% [2,357/2,549 patients] in the ribociclib + ET arm vs. 90.2% [2,304/2,552 patients] in the ET only arm).

Distant disease-free survival (DDFS)

As of DCO for the final iDFS HR for the secondary endpoint **DDFS** was 0.749 (95% CI 0.623, 0.900, nominal 1-sided p-value=0.0010) in favour of the ribociclib + ET arm. At DCO for the final iDFS analysis, 8.0% (204/2549) of the patients in the ribociclib + ET arm compared to 10.0% (256/2552) of the patients in the ET only arm had had an DDFS event. The estimated 3-year DDFS rates were 91.5% (95% CI 90.2, 92.7) and 88.9% (95% CI 87.4, 90.2) in the ribociclib + ET arm and the ET only arm, respectively. This translates into an absolute risk reduction of 2.6% in favour of ribociclib + ET treatment and is in line with the iDFS results of the primary analysis. As for RFS, the proportion of patients censored for DDFS was comparable between the two treatment arms (92.0% [2,345/2,549 patients] vs. 90.0% [2,296/2,552 patients] in the ribociclib + ET arm vs. the ET only arm).

Overall survival (OS)

At DCO for the final iDFS analysis, the median follow-up for the secondary endpoint **OS** was 35.9 months (range 0-52 months). At this time point, only 84 (3.3%) OS events had occurred in the ribociclib + ET arm compared to 88 (3.4%) OS events in the ET only arm. There was a trend for prolonged OS in the ribociclib + ET arm vs. the ET only arm, with HR=0.892 (95% CI 0.661, 1.203, nominal 1-sided p-value=0.2263). The 3-year OS rate was 97.0% (95% CI 96.2, 97.6) in the ribociclib + ET arm vs. 96.1% (95% CI 95.1, 96.9) in the ET only arm, respectively, translating into an absolute risk reduction of 0.9%. The total proportion of patients censored for OS was comparable between the ribociclib + ET arm and the ET only arm (96.7% [2,466/2,549 patients] vs. 96.5% [2,464/2,553 patients]).

Patient reported outcomes (PROs)

As regards the secondary endpoints **PROs**, the physical functioning sub-scale score of the EORTC QLQ-C30 was the primary PRO variable of interest. Secondary PRO variables were the Global health status/quality of life (QoL), emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale of the EORTC QLQ-BR23, the VAS scores of the EQ-5D-5L, and the anxiety domain and depression domain scores of HADS.

Overall, treatment with ribociclib + ET maintained PRO scores over time and completion rates for PRO questionnaires during the treatment period were comparable between both treatment arms. At baseline, PRO data was collected from 2,495 patients (97.9%) in the ribociclib + ET arm vs. 2,483 patients (97.3%) in the ET only arm. Among those patients, 84.5% of patients in the ribociclib + ET arm vs. 84.1% in the ET only arm partially completed the questionnaires at IA3. As of the DCO for IA3, data were collected for 469/544 patients (86.2%) in the ribociclib + ET arm vs. 502/610 patients (82.3%) in the ET only arm with a completed end of treatment visit. Of those patients with end of treatment PRO data, 67.7% of patients in the ribociclib + ET arm partially completed vs. 68.2% in the ET only arm at IA3.

Data regarding physical functioning using the EORTC QLQ-C30 were obtained at baseline, every 12 weeks during the first 24 months, every 24 weeks thereafter until confirmation of distant recurrence, at end of treatment, at confirmation of first recurrence and at confirmation of distant recurrence (if first recurrence was not distant), and every 12 weeks after distant recurrence for 12 months. Missing information were to be handled according to scoring manuals for each respective questionnaire. If >50% of the items were missing in a scale or subscale, the score for this scale/subscale would be considered missing for this assessment. Otherwise, the average of the non-missing items in the scale/subscale would be used to impute for the missing items when calculate the score for the scale/subscale.

Mean baseline physical functioning scores were well balanced between the treatment arms: 85.0 (on a scale of 0 to 100) in both the ribociclib plus ET and ET only arms. Physical functioning scores were generally similar between the two treatment arms throughout the study

Exploratory endpoints

Distant recurrence-free survival (DRFS)

A stratified Cox regression model was used to estimate the HR of the exploratory endpoint **DRFS**, a composite time to event endpoint of any distant recurrence or death) in a post-hoc analysis. At DCO for the final iDFS analysis, HR for **DRFS** was 0.738, (95% CI 0.606, 0.898, one-sided nominal p-value=0.0012), in favour of ribociclib + ET treatment. The DRFS distribution was estimated using the Kaplan-Meier method. There were 178 events in the ribociclib + ET arm vs. 227 events in the ET only arm.

Loco-regional recurrence-free survival (LRRFS)

At the DCO for IA3, HR for the exploratory endpoint **LRRFS** was 0.722 (95% CI 0.541, 0.962), 3.3% of the patients in the ribociclib + ET arm and 4.2% of the patients in the ET only arm had an LRRFS event. The 3-year LRRFS rates were 96.0% (95% CI 95.0, 96.8) in the ribociclib + ET arm and 93.0% (95% CI 91.2, 94.4) in the ET only arm.

At DCO for the final iDFS analysis, 612 patients (24.0%) in the ribociclib + ET arm and 693 patients (27.2%) in the ET only arm had discontinued all treatment components.

Post-treatment antineoplastic therapy

The proportion of patients who received at least one post-treatment antineoplastic medication was lower in the ribociclib + ET arm compared to the ET only arm (13.1% vs. 17.3%). The subsequent antineoplastic therapies included e.g., chemotherapy, ETs, EGFR and VEFGR inhibitors, HER2 inhibitors, mTOR inhibitors, PD-1/PD-L1 inhibitors, and investigational compounds. The only treatments

(summarised by treatment groups) received by ≥2% of the patients in any treatment arm were anti-oestrogens (.50% in the ribociclib + ET arm vs. 8.6% in the ET only arm), AIs (6.6% vs. 7.3%), CDK inhibitors (1.9% vs. 6.5%), GnRH analogues (1.4% vs. 2.6%), taxanes (1.5% vs. 2.5%), and pyrimidine analogues such as e.g., capecitabine and gemcitabine (2.5% vs. 3.1%). The frequency of use of post-treatment CDK4/6 inhibitors was 1.9% in the ribociclib + ET arm vs. 6.5% in the ET only group.

Health care resource utilisation

Regarding the exploratory endpoint **healthcare resource utilisation,** hospitalisation was reported for 14.7% of the patients in the ribociclib + ET arm (14.2% during on-treatment, 0.5% during follow-up) compared to 11.1% of the patients in the ET only arm (10.9% during on-treatment, 0.2% during follow-up). The median duration of on-treatment hospitalisation was five days in both treatment arms and two vs. one days for hospitalisation during follow-up for the ribociclib + ET arm vs. the ET only arm. (Data as of DCO for IA3.)

Ancillary analyses

Sensitivity analysis, primary endpoint iDFS

At DCO 11 Jan 2023 (IA3) an unstratified Cox regression model supported the result of the stratified model, with HR=0.759 (95% CI 0.627, 0.919) in favour of the ribociclib + ET arm. Results of the iDFS analysis based on the PPS were also consistent with the primary analysis based on the FAS (HR=0.749 [95% CI 0.618, 0.907], 1-sided p-value 0.0015).

Sensitivity analyses based on excluding missing iDFS assessment, backdating iDFS, new anti-cancer therapy, clinical recurrence, and death due to COVID-19, were supportive of the primary analysis results.

Table 32 Sensitivity analyses for iDFS assessment (data at IA3)

Sensitivity analysis	Treatment	n/N	p-value	Hazard ratio (95% CI)
Primary analysis	Ribociclib + ET	189/2549	0.0014	0.748 (0.618, 0.906)
	ET only	237/2552		
Primary analysis (PPS)	Ribociclib + ET	187/2496	0.0015	0.749 (0.618, 0.907)
	ET only	235/2424		
Primary analysis per CRF	Ribociclib + ET	189/2549	0.0012	0.744 (0.614, 0.901)
	ET only	237/2552		
Unstratified log-rank test and Cox model	Ribociclib + ET	189/2549	0.0023	0.759 (0.627, 0.919)
	ET only	237/2552		
Stratified Cox model adjusting for baseline covariates [a]	Ribociclib + ET	189/2549	0.0018	0.752 (0.621, 0.911)
	ET only	237/2552		
Actual event [b]	Ribociclib + ET	186/2549	0.0019	0.752 (0.620, 0.912)
	ET only	232/2552		
Backdating [c]	Ribociclib + ET	189/2549	0.0014	0.748 (0.618, 0.906)
	ET only	237/2552		
Censoring for antineoplastic therapy [d]	Ribociclib + ET	186/2549	0.0031	0.763 (0.629, 0.927)
	ET only	226/2552		
Clinical recurrence [e]	Ribociclib + ET	189/2549	0.0014	0.748 (0.618, 0.906)
	ET only	237/2552		
Censoring COVID death [f]	Ribociclib + ET	183/2549	0.0006	0.727 (0.600, 0.882)
	ET only	236/2552		

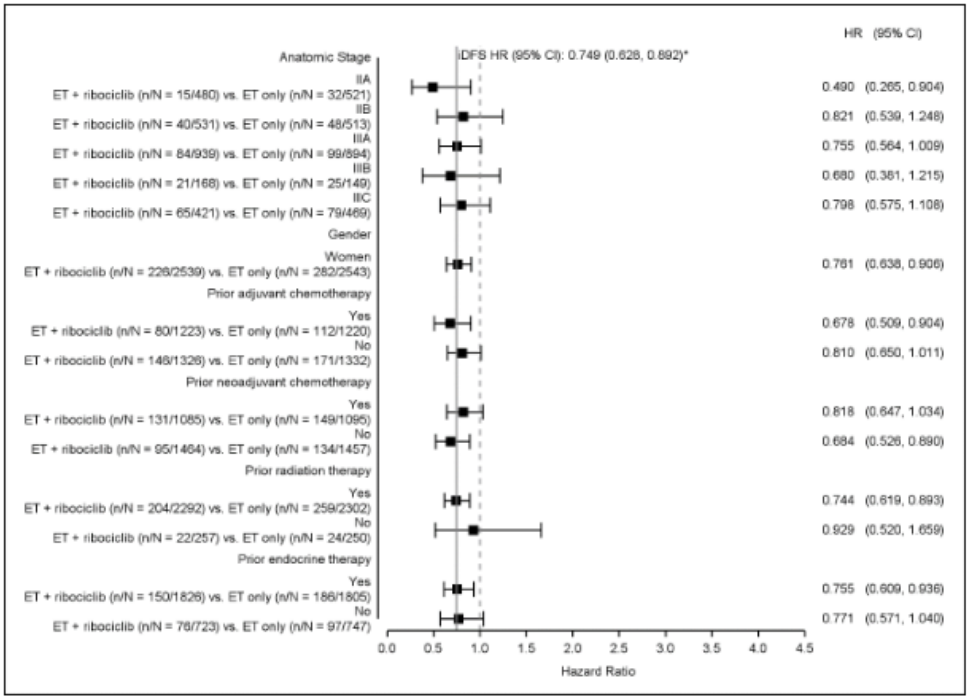
CI = Confidence interval.
[a] Baseline covariates included in the Cox proportional hazard model are Age category (<45, 45 - 54, and 55 - 64 vs. ≥65 years of age), ER/PR status (ER+/PR+ vs. other), and ET type (Letrozole vs. Anastrozole).
[b] Analysis excludes the event whenever it occurred after missing ≥ 2 tumor assessments during first 24 months or after missing ≥ 1 tumor assessment after the first 24 months.
[c] Analysis uses the date of the next scheduled assessment for events occurring after missing >= 1 assessment.
[d] Analysis performed by censoring patients at start of new antineoplastic therapy.
[e] Analysis considering treatment discontinuation due to disease recurrence as iDFS event without confirmation of recurrence.
[f] Analysis performed by censoring patients with COVID death as a measure of iDFS hazard ratio in a post COVID pandemic setting.
p-values were calculated based on log-rank test for [b],[c] and [d]. For [a], it is calculated based on wald test statistic of the hazard ratio.

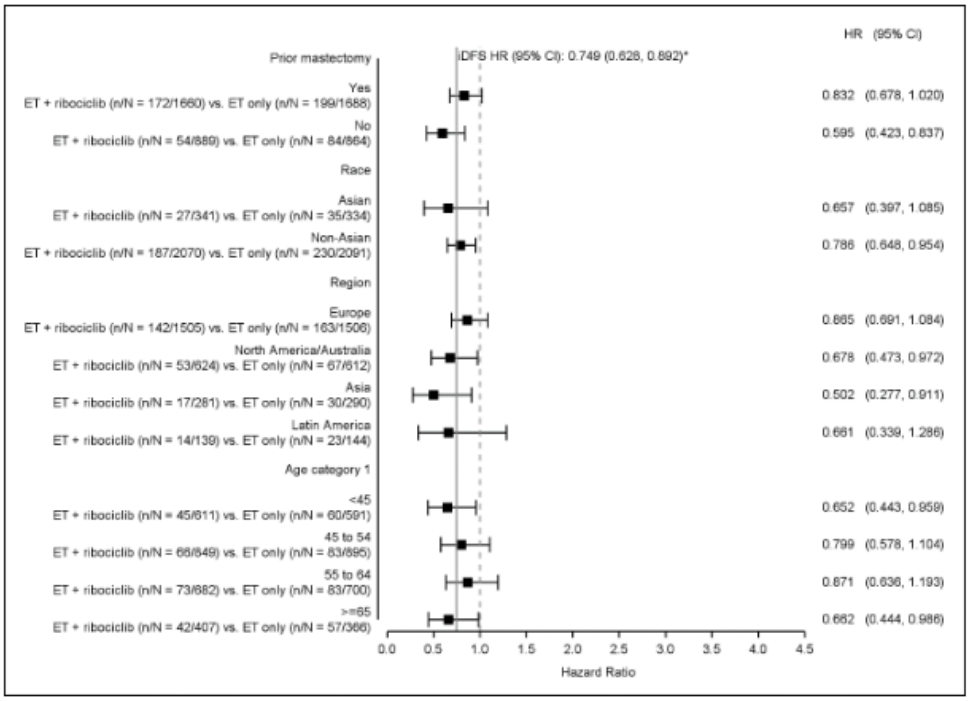
Subgroup analysis, primary endpoint iDFS

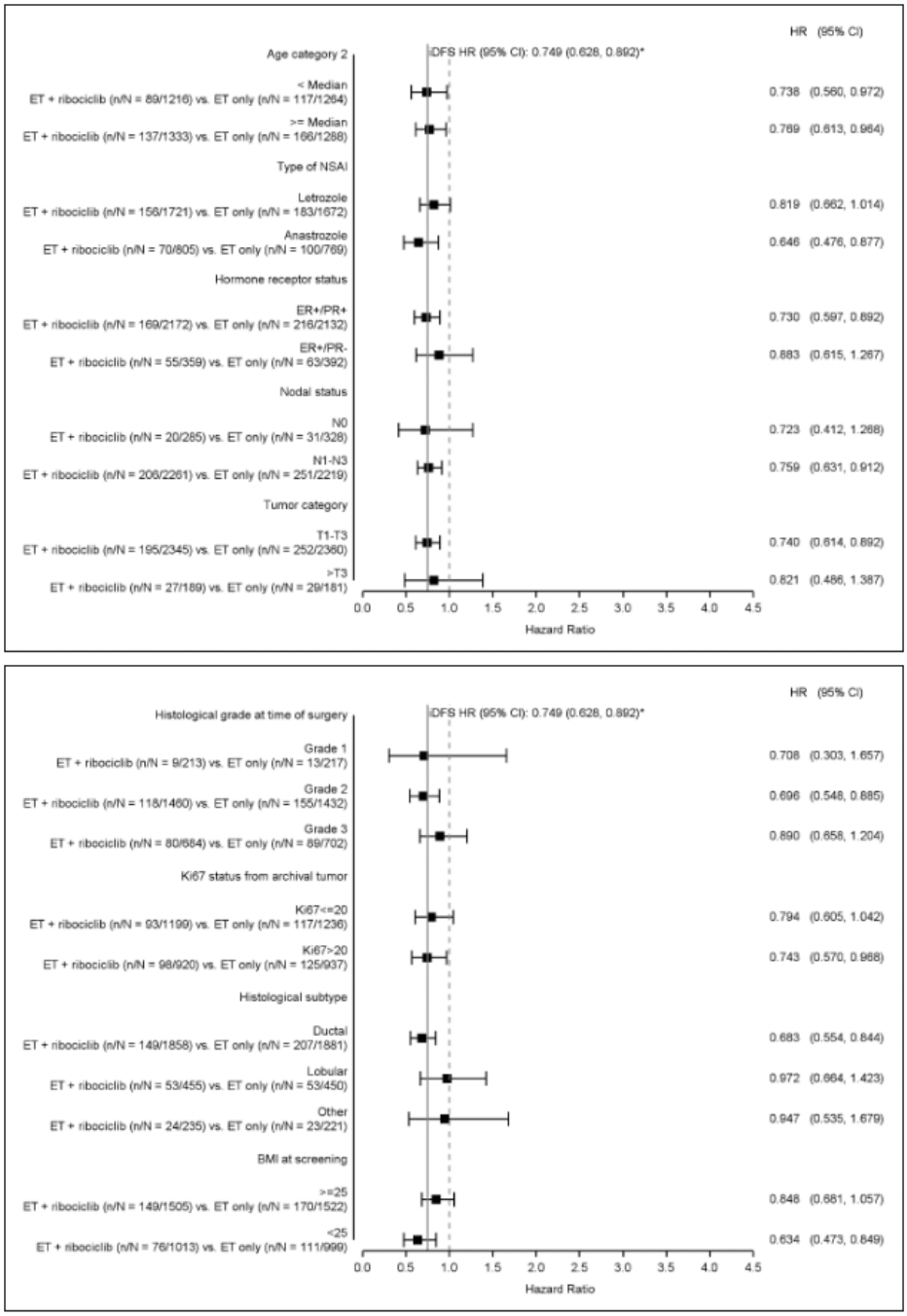
The primary efficacy endpoint iDFS was summarised by the following subgroups provided that the primary efficacy analysis based on the FAS was statistically significant:

- Stratification factor(s) (based on eCRF)
- Anatomic stages IIA, IIB, IIIA, IIIB, and IIIC (derived from eCRF data)
- Gender (women vs. men)
- Prior adjuvant chemotherapy (yes vs. no)
- Prior neoadjuvant chemotherapy (yes vs. no)
- Prior endocrine therapy (yes vs. no)
- Prior mastectomy (yes vs. no)
- Race (Asian vs. Non-Asian)
- Region (Europe, North America/Australia, Asia, Latin America)
- Age category 1 (<45 vs. 45-54 vs. 55-64 vs. ≥65)
- Age category 2 (<median vs. ≥median)
- Type of AI at randomisation (letrozole vs. anastrozole)
- ER+PR+ vs. ER-PR+ vs. ER+PR-
- Nodal status: N0 vs. N1-N3
- Tumour category: T0 vs. T1-T3 vs. > T3
- Histological grade at time of surgery: grade 1 vs. grade 2 vs. grade 3
- Ki67 status from surgical specimen: ≤20% vs. >20%. If the Ki67 score was missing from surgical specimen, the Ki67 score at initial diagnosis was considered.
- Histological subtype: ductal, lobular, other
- BMI at screening: ≥ 25 vs. < 25

Figure 13 Forest Plot of iDFS – subgroup analysis (final iDFS analysis, 21 Jul 2023 data cut-off) (FAS)







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

OS sensitivity analysis

Table 33 Sensitivity analyses of OS (final iDFS analysis, 21 Jul 2023 data cut-off) (FAS)

Sensitivity analysis	Treatment	n/N	p-value	Hazard ratio (95% CI)
Stratified analysis	ET + Ribociclib	84/2549	0.2263	0.892 (0.661, 1.203)
	ET only	88/2552		
Stratified analysis (PPS)	ET + Ribociclib	83/2496	0.2070	0.882 (0.654, 1.191)
	ET only	88/2423		
Stratified analysis per CRF	ET + Ribociclib	84/2549	0.1908	0.875 (0.648, 1.181)
	ET only	88/2552		
Unstratified log-rank test and Cox model	ET + Ribociclib	84/2549	0.2687	0.910 (0.675, 1.227)
	ET only	88/2552		
Stratified Cox model adjusting for baseline covariates [a]	ET + Ribociclib	84/2549	0.2567	0.905 (0.670, 1.221)
	ET only	88/2552		
Censoring COVID death [f]	ET + Ribociclib	78/2549	0.1262	0.837 (0.616, 1.136)
	ET only	87/2552		

CI = Confidence interval. P-values are based on stratified log-rank statistic. For [a], it is calculated based on wald test statistic of the hazard ratio.
[f] Analysis performed by censoring patients with COVID death as a measure of OS hazard ratio in the post COVID pandemic setting.

Summary of main study

The following table summarise the efficacy results from the main study 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).

Table 34 Summary of Efficacy for trial NATALEE, O12301C

Title: NATALEE, a phase III, open-label, randomised trial of ribociclib + ET versus ET only as adjuvant treatment of adult patients with HR-positive, HER2-negative, stage II or stage III early breast cancer, irrespective of nodal status.		
Study identifier	CLEE011O12301C EudraCT number 2018-002998-21 ClinicalTrials.gov identifier NCT03701334	
Design	Open-label, randomised, multi-centre phase III study. Patients were stratified for: • menopausal status (premenopausal women, and men vs. postmenopausal women) • AJCC 8th edition stage (stage II vs. stage III) • prior neoadjuvant/adjuvant chemotherapy (yes vs. no) • geographical region (North America/Western Europe/Oceania vs. rest of the world)	
	Duration of main phase:	7 Dec 2018 – ongoing
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Superiority of ribociclib + ET over ET only Statistical hypothesis: H_{01}: $\Theta_1 \geq 1$ vs. H_{A1}: $\Theta_1 < 1$ Θ_1 = iDFS HR (ricocilib + ET vs. ET only)		
Treatments groups	Ribociclib + ET arm		Ribociclib 400 mg (flat-fixed dose) was administered orally once daily on days 1-21 in each 28-day cycle. ET (letrozole or anastrozole) was administered orally once daily consecutively. Goserelin was administered subcutaneously on day 1±3 of each 28-day cycle to premenopausal women and to men for gonadal suppression. The ribociclib treatment duration was 36 months, unless discontinued earlier due to disease recurrence or intolerable toxicity. The ET treatment duration was 60 months. N=2,549 patients were randomised to receive ribociclib + ET.
	ET only arm		ET (letrozole or anastrozole) was administered orally once daily consecutively. Goserelin was administered subcutaneously on day 1±3 of each 28-day cycle to premenopausal women and to men for gonadal suppression. The ET treatment duration was 60 months. N=2,552 patients were randomised to receive ribociclib + ET.
Endpoints and definitions	Primary endpoint: invasive Disease-Free Survival	iDFS	The time from the date of randomisation to the date of the first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, contralateral invasive BC, a second primary non-breast invasive cancer (basal and squamous cell carcinomas of the skin excluded), or death due to any cause.
	Secondary endpoint, other: Relapse-Free Survival	RFS	The time from date of randomisation to date of first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence, or death due to any cause.
	Secondary endpoint, other: Distant Disease-Free Survival	DDFS	The time from date of randomisation to date of first event of distant recurrence, second primary non-breast invasive cancer (basal and squamous cell carcinomas of the skin excluded), or death due to any cause.

	Secondary endpoint, other: Overall Survival	OS	The time from randomisation to date of death due to any cause.
Database lock	IA3 11 Jan 2023, final iDFS analysis 21 Jul 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary population for efficacy analyses was the full analysis set (FAS), comprising all patients to whom study treatment had been assigned by randomisation regardless of whether treatment was administered or not. The primary analysis was conducted when approximately 426 iDFS events were observed. The primary endpoint iDFS was alpha protected. P-values for secondary endpoints are nominal.		
Effect estimates per comparison	Primary endpoint iDFS, data at IA3 (inferential analysis)	Ribociclib + ET vs. ET only	N=2,549 patients in the ribociclib + ET arm N=2,552 patients in the ET only arm
		Cox regression	HR=0.748
		95% CI	0.618, 0.906
		P-value 1-sided, Log-Rank test	0.0014
	Primary endpoint iDFS, final iDFS analysis	Ribociclib + ET vs. ET only	
		Cox regression	0.749
		95% CI	0.628, 0.892
		P-value 1-sided, Log-Rank test	0.0006
	Secondary endpoint RFS (data at final iDFS analysis)	Ribociclib + ET vs. ET only	
		Cox regression	HR=0.727
		95% CI	0.602, 0.887
		P-value 1-sided, Log-Rank test	0.0004 (Not type 1 error controlled)
	Secondary endpoint DDFS (data at final iDFS analysis)	Ribociclib + ET vs. ET only	
		Cox regression	HR=0.79

		95% CI	0.602, 0.900
		P-value 1-sided, Log-Rank test	0.0010 (Not type 1 error controlled)
	Secondary endpoint OS (data at final iDFS analysis)	Ribociclib + ET vs. ET only	
		Cox regression	HR=0.892
		95% CI	0.661, 1.203
		P-value 1-sided, Log-Rank test	0.2263 (Not type 1 error controlled)

Clinical studies in special populations

	Controlled trials **CLEE011O12301C (NATALEE), Safety set**
Renal impairment* patients (Subjects number/total number)	23/4967
Hepatic impairment patients (Subjects number/total number)**	109/4967
Paediatric patients <18 years (Subjects number/total number)	Not Applicable
Age 65-74 (Subjects number/total number)	634/4967
Age 75-84 (Subjects number/total number)	116/4967
Age 85+ (Subjects number/total number)	3/4697

*Renal impairment is defined as having CKD Stage 3b, 4, or 5 (KDIGO definition)

**Hepatic impairment is defined as having Child-Pugh score B or C

2.4.1. Discussion on clinical efficacy

2.4.1.1. Design and conduct of clinical study

Data to support the current application are derived from the multi-centre, open-label, phase III study CLEE011O12301C (NATALEE), conducted in 393 centres across 20 countries world-wide.

Overall, the study entry criteria in the pivotal study define an appropriate population for the proposed treatment. The comparator arm contains a standard of care AI for the indicated population. The open-label design is considered appropriate since it would be functionally difficult to blind a study where the

add-on treatment in the experimental arm has a fundamentally different toxicity profile than the treatment in the comparator arm. A justification of the decision to the open-label design of the trial was added to the CSP version 2.0 (20 June 2019) following a scientific advice received from CHMP.

Patients were randomised to receive either ribociclib + an *aromatase inhibitor* (AI) (hereafter ET [endocrine therapy]) or ET only. Ribociclib + ET or ET only were administered orally with or without food. Ribociclib was administered as a flat-fixed dose of 400 mg orally on days 1-21 in each 28-day cycle. ETs (letrozole or anastrozole) were administered orally once daily continuously. Men and premenopausal women also received the GnRH agonist goserelin for gonadal suppression.

Randomisation used an allocation ratio 1:1 and was stratified by menopausal status, AJCC 8th edition Anatomic Stage Group, prior neo-/adjuvant chemotherapy, and geographical region. The proposed (and maintained) stratified randomisation was supported in a CHMP scientific advice.

Ribociclib treatment was scheduled for 36 months, unless discontinued earlier due to disease recurrence or unacceptable toxicity. ET treatment was scheduled for at least 60 months from randomisation, but adjuvant ET was allowed up to 12 months before study enrolment. Hence, ET treatment in both treatment arms could begin prior to ribociclib treatment.

The primary endpoint was iDFS (alpha protected) and secondary endpoints included RFS, DDFS, and OS (not alpha protected). All endpoints were investigator-assessed. The endpoints are considered relevant time-dependent endpoints in a Randomized Clinical Trial. Other secondary endpoints were PROs.

After the study had started, the assumptions and expectations underlying the sample size estimation were changed twice (CSP version 2.0, 20 June 2019 and CSP version 4.0, 27 August 2020). The rationale for a minor change in expected Anatomic stage distribution and a decision to exclude Anatomic Stage II low risk patients (with CSP version 2.0) and discussions concerning the heterogeneity of the study population was addressed in the CHMP scientific advice This change is considered to have been implemented early in the study (approximately 5 months after randomisation of the first patient) and given the background, is not objected to. However, this also had an impact on study power, targeted number of iDFS event as well as primary analysis time-point.With CSP version 4.0, a decision was made to randomise an additional 1,000 Stage III patients implying that the total sample size was increased from initial 4,000 to 5,000.

Patients were randomised between 10 January 2019 and 20 April 2021. The projected proportion of Stage II patients as per CSP version 2.0 (approximately 50%) had already been reached when it was decided to increase the number of Stage III patients. This explains why the distribution of Anatomic Stage II and Stage III patients ended up as had been initially planned (40%/60%).

The applicant's justification for increasing the number of Stage III patients was emergent external data. The applicant referred to new data from PALLAS and MonarchE trials, where preliminary results indicated that patients with stage III early BC may have an increased treatment benefit from CDK4/6 inhibitors compared to patients with Stage II early BC. This is acknowledged.

Further, a third interim analysis (IA) was added and the number of iDFS events for the final analysis was at the same time increased from 375 to 500. It would have been preferred to delete the second/altering the timing of the already planned second efficacy IA instead of only adding a third IA. The number of IAs to be performed in a study should always be kept at a minimum.

Based on sufficiently convincing statistical evidence in the primary analysis and a justification based on external data, there are no specific concerns regarding the risk for study integrity damage and loss of type I error control.

The first IA had a futility objective only and can be accepted. IAs 2 and 3 were both intended to declare superior efficacy of the experimental arm.

IA 3 was planned to occur at 85% information fraction and was performed after 426 iDFS events. Based on the outcome, the independent DMC concluded that the study met its primary endpoint. This is the analysis presented within this submission as the primary efficacy endpoint analysis.

Regarding secondary endpoints and multiplicity considerations, no multiple testing procedure had been planned except for the considerations made in relation to the multiple analysis over time of the primary endpoint. In this respect it is endorsed that no additional claims besides for the primary endpoint are included in the SmPC.

The primary analysis was based on FAS (all randomised patients). The primary testing and estimation were based on a stratified log rank test and an adjusted Cox proportional hazard regression model, both test and estimation accounting for the stratification factors used at randomisation. The primary analysis of the primary endpoint is thus endorsed. Censoring rules were appropriate.

All endpoints were investigator-assessed. As stated in the scientific advice in 2016, this was not agreed upon. All efforts must be made to keep the strictest parallelism in the assessments between arms to minimise the risk of bias when the study is not double-blinded. However, the majority of recurrence events were histologically or cytologically confirmed, thus providing objective confirmation of the events. This is acknowledged.

2.4.1.2. Efficacy data and additional analyses

In total, 6,068 patients were screened, and 5,101 patients (84.0%) were included in study O12301C.

Of the 5,101 patients included, 2,549 and 2,552 patients were randomised to receive ribociclib + ET vs. ET only treatment, respectively. Overall, the proportion of patients receiving the allocated treatments were equally high, 99.1% and 95.7% in the ribociclib + ET arm vs. the ET only arm, respectively.

At DCO for IA3, 542 patients (21.3%) in the ribociclib + ET arm and 616 patients (24.1%) in the ET only arm had discontinued all treatment, respectively. Disease relapse as reason for treatment discontinuation was low in both treatment arms (4.3% and 5.6% discontinuations of ribociclib and ET treatments, respectively, in the ribociclib + ET arm vs. 7.3% ET discontinuations in the ET only arm).

At DCO for IA3, 1,984 patients (77.8%) in the ribociclib + ET arm and 1,826 patients (71.6%) in the ET only arm were still on study treatment. This difference between the treatment arms is expected, provided that the add-on treatment in the experimental arm is effective. Consequently, study discontinuation due to death was infrequent in both treatment arms (2.4% and 2.9%, respectively). Furthermore, at DCO, 20.2% patients in the ribociclib + ET arm had completed three years of ribociclib treatment and 57.4% had completed two years of treatment.

As of DCO of final iDFS analysis, with an additional median 6.3 months follow-up, in total 1,996 patients (78.3%) in the ribociclib + ET arm had discontinued ribociclib, of which 1,091 patients (42.8%) had completed the 3-year treatment duration and 905 patients (35.5%) had discontinued ribociclib prematurely. The main reason for early discontinuation was AE (19.5%).

In total, at least one protocol deviation was reported for 70.2% of the patients. The percentage of patients with deviations was slightly higher in the ribociclib + ET arm compared to that in the ET only arm (73.3% vs. 67.1%). The difference between treatment arms was mainly due to a higher number of dosing and administration errors in the ribociclib + ET arm compared to the ET only arm (25.9% vs. 14.5%). This could be understood given that the ribociclib + ET arm consisted of two different medications, of which ribociclib was administered during a 3 weeks on/1 week off schedule, and the ET only arm consisted of only one medication administered continuously. Overall, only 47 patients (0.9%) were excluded from the PPS due to major deviations. A numerical imbalance between the treatment arms was, however, also noted for protocol deviations due to prohibitive medication/treatment, with 304

(11.9%) such reported deviations in the ribociclib + ET arm vs. 51 (2.0%) in the ET only arm. The Applicant confirmed that there were more protocol-defined prohibited medications with ribociclib than with ET, explaining the noted imbalance between the study arms. The duration of the prohibited concomitant medication was generally less than seven days and without noticeable imbalance between the study arms, indicating that there was no impact on the supportive iDFS. This explanation is accepted.

There was a slight imbalance in COVID-19 pandemic-related deviations, with fewer such deviations being reported in the ribociclib + ET arm (16.6%) compared to the ET only arm (23.2%). The Applicant has not provided any reasons for this, but regardless of treatment arm the main pandemic-related deviation was due to `planned visits not being done at sites´, which is acknowledged.

Overall, the baseline demographic and disease characteristics were well balanced between the two treatment arms. The median age (52.0 years) and gender distribution (99.6% women, 0.4% men) were identical in the treatment arms. Per protocol, patients were followed until distant recurrence event even if the patient initiated a new anti-neoplastic treatment.

Previous cancer therapies, including prior chemotherapy, ET, radiotherapy, and surgery were comparable between the treatment arms.

The study met its primary endpoint, demonstrating a statistically significant improvement of iDFS in favour of ribociclib + ET treatment, with HR=0.748 (95% CI 0.618, 0.906, 1-sided p-value=0.0014) in favour of ribociclib + ET treatment. When it regards adjuvant treatment of a patient population with an overall favourable prognosis (long expected OS) it may be more relevant to compare the absolute difference between treatment arms rather than medians. In the current study, the absolute iDFS improvement with ribociclib + ET treatment at 3-years was 3.3% (3-year iDFS rates 90.4% [95% CI 88.6, 91.9] in the ribociclib + ET arm and 87.1% [95% CI 85.3, 88.8] in the ET only arm). This is in line with what is normally accepted in adjuvant trials. Due to the limited number of patients that had completed three years of ribociclib treatment, though, the 3-year iDFS improvement must be interpreted with caution.

Although only 42.8% of the patients had completed the intended 3-year ribociclib treatment and 20.7% of the patients were still on ribociclib treatment, in total almost 80% had discontinued ribociclib and there were no signs of a rebound peak with relapses shortly after end of treatment. Apart from completion of the intended 3-year treatment, the most common reason for ribociclib discontinuation was AEs (19.5%).

Overall, the sensitivity analyses were supportive of the primary analysis results. For the subgroup analyses, the objective was to demonstrate homogeneity of treatment effect, but no formal statistical hypothesis testing was performed. It is noted that the upper boundary of the confidence interval was crossing 1.0 for several subgroups (e.g., several substages, age categories 45-54 and 55-64 years, ER+/PR- tumours, >T3, and grade 1) but the number of events in all these subgroups were very limited. The HR point estimates were all <1.0. The subgroup analyses should be interpreted with caution, but the data do not raise any concerns regarding a detrimental effect of ribociclib in any subgroup.

Inclusion of stage II patients was capped at 40% in line with scientific advice received in 2018 where it was highlighted that consistent responses across stages would be crucial to justify that the observed study results can be generalised to the overall patient population outside clinical trials. Although subgroup analyses of stages II and III revealed that the upper boundary of the confidence interval was crossing 1.0 for stages IIB, IIIA, and IIIB, it did not for stages IIA and IIIC. In light of the HR point estimates being <1.0 and the limited number of events in all substages, there is no concern about a detrimental effect of ribociclib in any substage. Overall, no obvious difference in response to ribociclib between stages II and III was noted.

Improvements of the secondary endpoints RFS (HR=0.727 [95% CI 0.602, 0.887], nominal 1-sided p-value=0.0004) and DDFS (HR=0.749 [95% CI 0.602, 0.900], nominal 1-sided p-value=0.0010) at DCO

for final iDFS analysis imply a potential clinical relevance, supported by absolute 3-year risk reductions of 3.0%, for RFS and 2.26 for DDFS, respectively, in favour of ribociclib + ET treatment. This is in line with the primary analysis. It is, however, noted that none of the secondary endpoints were type I error controlled.

OS data were immature at DCO for final iDFS analysis, with only 3.3% and 3.4% events (n=84 and n=88 patients) in the ribociclib + ET arm and the ET only arm, respectively. Data indicated a trend for prolonged OS in the ribociclib + ET arm vs. the ET only arm, with HR=0.892 (95% CI 0.661, 1.203, nominal 1-sided p-value=0.2263). The 3-year OS rates indicate an absolute risk reduction of 0.9% for ribociclib + ET over ET only.

To better characterize the efficacy profile of ribociclib in the current indication the MAH has committed to submit 5-year iDFS and OS data as a post approval measure (PAES Annex IID condition) according to delegated act: (a) an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions

Overall, treatment with ribociclib + ET maintained PRO scores over time. PRO data should, however, be interpreted with caution due to the open-label study design, due to the PRO endpoints not being type 1 error controlled, and the fact that the patients answered the PRO questionnaires on day one of every third treatment cycle (i.e., after one week off ribociclib).

At DCO of the final iDFS analysis, 13.1% of the patients in the ribociclib + ET arm compared to 17.3% of the patients in the ET only arm had received at least on post-treatment antineoplastic therapy. The range of subsequent antineoplastic therapies was wide, with only few patients reported to have received the different treatments.

Following the CHMP review of this extension of indication application, the agreed indication is:

Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 for selection criteria).

2.4.2. Conclusions on the clinical efficacy

The initial study protocol included stage II and stage III eBC, however, as the protocol was eventually modified to exclude patients with low risk of recurrence stage II, the actually studied population can be considered reflecting a high-risk of recurrence population, which is reflected in the agreed indication.

A statistically significant effect on iDFS has been shown for ribociclib + ET in the intended patient population, supported by RFS and DDFS results.

With a median follow-up of 33.3 months, a 3.1% absolute improvement in iDFS at three years, no signs of a relapse peak shortly after treatment discontinuation but rather iDFS curves that continue to separate over time, the treatment effect on iDFS is considered robust and the remaining uncertainty pertaining to an effect on OS is considered acceptable. However more mature OS and IDFS data are considered critical to characterize the long-term benefit of ribociclib.

Therefore, the applicant has committed to submit 5-year follow-up for efficacy and safety including OS data in the final study report for the NATALEE study.

This has been reflected in the RMP and Annex II: Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of Kisqali in combination with an aromatase inhibitor for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2

(HER2)-negative early breast cancer at high risk of recurrence, the MAH should submit a 5-year follow-up of iDFS and OS in the NATALEE study.

2.5. Clinical safety

2.5.1. Introduction

The most common ADRs that have previously been established for ribociclib include those related to bone marrow suppression (notably neutropenia), infections, GI-disorders, alopecia, hepatotoxicity and the risk of QT-prolongation.

The safety specification in the RMP (version 8.0) include myelosuppression, hepatobiliary toxicity, QT interval prolongation and reproductive toxicity as important identified risks and renal toxicity as an important potential risk.

The safety data presented in this report derive from study CLEE011O12301C (acronym NATALEE) and are based on an updated data cut-off date of 21-Jul-2023 unless otherwise indicated. The Safety set included all randomized patients who received any study treatment (i.e., at least one dose of ribociclib or ET). Patients were analyzed according to the study treatment received.

The evaluation is based on safety data from 2525 patients exposed to a starting dose of 400 mg ribociclib once daily on Day 1 to Day 21 of each 28-day cycle in combination with ET (letrozole or anastrozole [NSAI]) and 2444 patients exposed to ET only (plus goserelin, if applicable, in both groups).

2.5.2. Patient exposure

In the NATALEE study, 400 mg ribociclib was to be administered once daily on Day 1 to Day 21 in each 28-day cycle for a 3-year treatment duration. ET was to be administered for at least a 5-year treatment duration in both the ribociclib + ET and ET only groups.

There were 1752 patients (69.4%) who completed at least two years of ribociclib treatment. Of these, 1091 patients (43.2%) had at least three years of ribociclib. In detail, the following exposure data by drug component were observed:

• The median duration of exposure to ribociclib was 32.9 months (range: 0 to 37)

• The median duration of exposure to NSAI was 36.0 months (range: 0 to 54) in the ribociclib plus ET group and the ET only group, 35.9 months (0 to 54)

• The median duration of exposure to goserelin was 33.8 months (range: 0 to 52) in the ribociclib plus ET group and in ET only group, 31.3 months (0 to 52)

• The median RDI for ribociclib was 94.0% (range: 14 to 132)

• The median RDI for NSAI was 100.0% in both treatment groups (ribociclib plus ET, range: 21 to 127; ET only, range: 4 to 105)

• The median RDI for goserelin was 99.7% in both treatment groups (ribociclib plus ET, range: 34 to 1395; ET only, range: 48 to 399)

Table 35. Duration of exposure and adherence by drug component (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

		NSAI		Goserelin	
Study treatment adherence	Ribociclib N=2525	Ribociclib plus ET N=2525	ET only N=2442	Ribociclib plus ET N=1102	ET only N=1066
Duration of exposure (n (%))					
0 to 3 months	305 (12.1)	126 (5.0)	170 (7.0)	70 (6.4)	89 (8.3)
3 to 6 months	164 (6.5)	85 (3.4)	77 (3.2)	46 (4.2)	51 (4.8)
6 to 9 months	89 (3.5)	56 (2.2)	51 (2.1)	31 (2.8)	29 (2.7)
9 to 12 months	51 (2.0)	47 (1.9)	55 (2.3)	25 (2.3)	33 (3.1)
12 to 15 months	47 (1.9)	39 (1.5)	44 (1.8)	24 (2.2)	26 (2.4)
15 to 18 months	37 (1.5)	36 (1.4)	47 (1.9)	24 (2.2)	37 (3.5)
18 to 21 months	44 (1.7)	44 (1.7)	56 (2.3)	24 (2.2)	37 (3.5)
21 to 24 months	36 (1.4)	35 (1.4)	31 (1.3)	35 (3.2)	27 (2.5)
24 to 27 months	46 (1.8)	26 (1.0)	28 (1.1)	47 (4.3)	32 (3.0)
27 to 30 months	267 (10.6)	293 (11.6)	267 (10.9)	125 (11.3)	126 (11.8)
30 to 33 months	211 (8.4)	113 (4.5)	119 (4.9)	70 (6.4)	68 (6.4)
33 to 36 months	1205 (47.7)	345 (13.7)	301 (12.3)	172 (15.6)	134 (12.6)
36 to 39 months	23 (0.9)	232 (9.2)	205 (8.4)	112 (10.2)	95 (8.9)
		NSAI		Goserelin	
Study treatment adherence	Ribociclib N=2525	Ribociclib plus ET N=2525	ET only N=2442	Ribociclib plus ET N=1102	ET only N=1066
39 to 42 months	0	441 (17.5)	411 (16.8)	129 (11.7)	116 (10.9)
42 to 45 months	0	367 (14.5)	341 (14.0)	104 (9.4)	113 (10.6)
45 to 48 months	0	197 (7.8)	191 (7.8)	56 (5.1)	45 (4.2)
48 to 51 months	0	34 (1.3)	39 (1.6)	7 (0.6)	5 (0.5)
51 to 54 months	0	9 (0.4)	8 (0.3)	1 (0.1)	3 (0.3)
54 to 57 months	0	0	1 (< 0.1)	0	0
Duration of exposure (months)					
n	2525	2525	2442	1102	1066
Mean	25.4	32.7	31.8	29.7	28.1
SD	13.16	12.86	13.68	13.13	13.93
Min	0	0	0	0	0
Median	32.9	36.0	35.9	33.8	31.3
Max	37	54	54	52	52
Cumulative dose (mg)					
n	2525	2525	2442	1102	1066
Mean	201613.3	2021.8	1987.5	114.9	108.7
SD	116021.77	1077.53	1104.01	51.24	54.18
Min	400	1	1	4	4
Median	238400.0	2202.5	2190.0	129.6	122.4
Max	658000	4085	5410	202	198
Dose intensity (mg/day)					
n	2525	NA	NA	1102	1066
Mean	333.7	NA	NA	0.1	0.1
SD	78.74	NA	NA	0.06	0.02
Min	56	NA	NA	0	0
Median	375.8	NA	NA	0.1	0.1
Max	527	NA	NA	2	1
Relative dose intensity (%)					
n	2525	2525	2442	1102	1066
Mean	83.4	99.0	99.2	101.6	100.4
SD	19.69	3.57	3.84	45.62	18.29
Min	14	21	4	34	48
Median	94.0	100.0	100.0	99.7	99.7
Max	132	127	105	1395	399
Average daily dose (mg)					
n	2525	2525	2442	1102	1066
Mean	366.0	2.0	2.1	3.6	3.6
SD	66.35	0.68	0.67	0	0
Min	201	1	1	4	4
Median	400.0	2.5	2.5	3.6	3.6
Max	438	3	3	4	4

Study treatment adherence	Ribociclib N=2525	NSAI Ribociclib plus ET N=2525	NSAI ET only N=2442	Goserelin Ribociclib plus ET N=1102	Goserelin ET only N=1066

Duration of exposure for ribociclib is calculated as (last date of ribociclib) – (first date of ribociclib) + 1.
Duration of exposure for NSAI and Goserelin is calculated as (last date of exposure) - (first date of exposure) + 1. The first date of exposure is defined as the date of first administration of any NSAI or of Goserelin. The last date of exposure for letrozole and anastrozole is defined as the date of last administration of any ET during the study. The last date of exposure for Goserelin is defined as the date of last administration of Goserelin + 27 days. If a patient died or was lost to follow-up within date of last administration + 27 days, then the last date of exposure is the date of death or last contact date, respectively.
Actual cumulative dose for NSAI is the sum of the number of tablets in mg taken per day over the dosing period. Actual cumulative dose for ribociclib and Goserelin is defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods.
Dose intensity (DI) is defined as DI=actual cumulative dose / duration of exposure, where adjusted duration of exposure is used for ribociclib due to its 3 weeks on and 1 week off dosing schedule.
NSAI dose intensity is used to derive NSAI relative dose intensity, but actual dose intensity for NSAI is not displayed since Anastrozole and Letrozole are pooled together under NSAI and have different prescribed doses (1.0 mg/day for Anastrozole and 2.5 mg/day for Letrozole).
Relative dose intensity (RDI) is defined as RDI=DI/PDI, where PDI is planned dose intensity and PDI=planned cumulative dose / duration of exposure, where adjusted duration of exposure is used for ribociclib. PDI for ribociclib is 400 mg/day, PDI for letrozole is 2.5mg/day, PDI for anastrozole is 1 mg/day, and PDI for Goserelin is 0.129 mg/day.

2.5.3. Adverse events

2.5.3.1. Overview of adverse events

Table 36. Overall summary of deaths and adverse events (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

AE category	Ribociclib plus ET N=2525 All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	ET only N=2442 All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All deaths[1]	83 (3.3)	–	–	–	89 (3.6)	–	–	–
On-treatment deaths[2]	20 (0.8)	–	–	–	9 (0.4)	–	–	–
Adverse events	2474 (98.0)	1463 (57.9)	133 (5.3)	11 (0.4)	2145 (87.8)	425 (17.4)	40 (1.6)	4 (0.2)
Suspected to be drug-related	2368 (93.8)	1284 (50.9)	101 (4.0)	1 (< 0.1)	1566 (64.1)	97 (4.0)	6 (0.3)	0
Serious adverse events	357 (14.1)	252 (10.0)	44 (1.7)	11 (0.4)	256 (10.5)	192 (7.9)	26 (1.1)	4 (0.2)
Suspected to be drug-related	68 (2.7)	39 (1.5)	17 (0.7)	1 (< 0.1)	13 (0.5)	9 (0.4)	0	0
AEs leading to discontinuation	524 (20.8)	201 (8.0)	36 (1.4)	2 (0.1)	134 (5.5)	38 (1.6)	5 (0.2)	3 (0.1)
Suspected to be drug-related	435 (17.2)	165 (6.5)	26 (1.0)	0	94 (3.9)	18 (0.7)	0	0
AEs requiring dose interruption	1858 (73.6)	1226 (48.6)	87 (3.5)	0	199 (8.2)	67 (2.7)	8 (0.3)	0
Suspected to be drug-related	1635 (64.8)	1156 (45.8)	70 (2.8)	0	99 (4.1)	27 (1.1)	3 (0.1)	0
AEs requiring dose adjustment	586 (23.2)	338 (13.4)	36 (1.4)	0	–	–	–	–
Suspected to be drug-related	561 (22.2)	330 (13.1)	36 (1.4)	0	–	–	–	–
AEs requiring additional therapy	1962 (77.7)	499 (19.8)	61 (2.4)	2 (0.1)	1627 (66.6)	297 (12.2)	28 (1.2)	1 (< 0.1)
Suspected to be drug-related	1225 (48.5)	240 (9.5)	32 (1.3)	0	696 (28.5)	58 (2.4)	3 (0.1)	0
AEs of special interest	2183 (86.5)	1291 (51.1)	114 (4.5)	7 (0.3)	1179 (48.3)	168 (6.9)	15 (0.6)	2 (0.1)
Suspected to be drug-related	1886 (74.7)	1188 (47.1)	100 (4.0)	0	203 (8.3)	17 (0.7)	2 (0.1)	0

[1] All deaths including those not considered on-treatment deaths. Includes deaths with cause other than AE. Deaths due to disease progression or other are listed in the all grades column.
[2] On-treatment deaths are defined as occurring on or after treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation. Deaths due to disease progression or other are listed in the all grades column.
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.
Patients are counted once / category at worst toxicity grade in the main category rows and once per category per toxicity in the related rows.

A total of 98 % of patients in the ribociclib + ET group and 87.8% of patients in the ET only group experienced at least one AE during the study.

In terms of All Deaths, 83 (3.3%) and 89 (3.6%) died in the test-arm and control arm, respectively. Corresponding numbers for On-treatment Deaths (defined as deaths occurring on or after treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation and include deaths with cause other than AE), were 20 patients (0. 7%) in the ribociclib + ET group and nine patients (0.4%), respectively.

Table 37. Adverse events by primary system organ class and maximum grade, irrespective of causality (final iDFS analysis, 21-Jul-2023) data cut-off (Safety set)

	Ribociclib plus ET // N=2525				ET only // N=2442			
System organ class	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Total no. patients with at least 1 TEAE	**2474 (98.0)**	**1463 (57.9)**	**133 (5.3)**	**11 (0.4)**	**2145 (87.8)**	**425 (17.4)**	**40 (1.6)**	**4 (0.2)**
Investigations	1634 (64.7)	640 (25.3)	67 (2.7)	0	795 (32.6)	72 (2.9)	10 (0.4)	0
Musculoskeletal and connective tissue disorders	1539 (61.0)	60 (2.4)	1 (< 0.1)	0	1567 (64.2)	56 (2.3)	0	0
General disorders and administration site conditions	1386 (54.9)	55 (2.2)	0	0	902 (36.9)	22 (0.9)	0	0
Gastrointestinal disorders	1321 (52.3)	59 (2.3)	1 (< 0.1)	0	724 (29.6)	32 (1.3)	0	0
Infections and infestations	1249 (49.5)	124 (4.9)	8 (0.3)	6 (0.2)	878 (36.0)	72 (2.9)	3 (0.1)	2 (0.1)
Blood and lymphatic system disorders	1217 (48.2)	707 (28.0)	35 (1.4)	0	217 (8.9)	23 (0.9)	3 (0.1)	0
Nervous system disorders	1013 (40.1)	53 (2.1)	5 (0.2)	1 (< 0.1)	788 (32.3)	40 (1.6)	4 (0.2)	0
Skin and subcutaneous tissue disorders	942 (37.3)	12 (0.5)	1 (< 0.1)	0	495 (20.3)	10 (0.4)	0	0
Vascular disorders	832 (33.0)	72 (2.9)	0	0	818 (33.5)	67 (2.7)	1 (< 0.1)	0
Metabolism and nutrition disorders	755 (29.9)	34 (1.3)	2 (0.1)	0	367 (15.0)	24 (1.0)	4 (0.2)	0
Respiratory, thoracic and mediastinal disorders	733 (29.0)	41 (1.6)	4 (0.2)	2 (0.1)	432 (17.7)	25 (1.0)	3 (0.1)	1 (< 0.1)
Psychiatric disorders	616 (24.4)	12 (0.5)	4 (0.2)	0	571 (23.4)	10 (0.4)	7 (0.3)	0
Injury, poisoning and procedural complications	375 (14.9)	44 (1.7)	1 (< 0.1)	1 (< 0.1)	301 (12.3)	37 (1.5)	0	0
Reproductive system and breast disorders	357 (14.1)	19 (0.8)	1 (< 0.1)	0	403 (16.5)	15 (0.6)	0	0
Eye disorders	313 (12.4)	10 (0.4)	1 (< 0.1)	0	172 (7.0)	10 (0.4)	0	0
Cardiac disorders	197 (7.8)	18 (0.7)	3 (0.1)	2 (0.1)	156 (6.4)	19 (0.8)	1 (< 0.1)	2 (0.1)
Renal and urinary disorders	176 (7.0)	12 (0.5)	1 (< 0.1)	0	124 (5.1)	4 (0.2)	0	0
Ear and labyrinth disorders	154 (6.1)	5 (0.2)	0	0	91 (3.7)	4 (0.2)	1 (< 0.1)	0
Hepatobiliary disorders	124 (4.9)	25 (1.0)	11 (0.4)	0	77 (3.2)	9 (0.4)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	113 (4.5)	30 (1.2)	4 (0.2)	0	115 (4.7)	24 (1.0)	8 (0.3)	0
Endocrine disorders	56 (2.2)	1 (< 0.1)	0	0	71 (2.9)	1 (< 0.1)	1 (< 0.1)	0
Immune system disorders	43 (1.7)	2 (0.1)	0	0	32 (1.3)	2 (0.1)	0	0
Product issues	3 (0.1)	2 (0.1)	0	0	4 (0.2)	1 (< 0.1)	0	0
	Ribociclib plus ET // N=2525				ET only // N=2442			
System organ class	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Congenital, familial and genetic disorders	3 (0.1)	1 (< 0.1)	0	0	4 (0.2)	1 (< 0.1)	0	0
Social circumstances	0	0	0	0	2 (0.1)	0	0	0

System organ classes are sorted in descending frequency based on frequency in ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.

Table 38. Adverse events by preferred term and maximum grade (all grades ≥ 2% / either group), irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

	Ribociclib plus ET // N=2525				ET only // N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Neutropenia	1047 (41.5)	673 (26.7)	34 (1.3)	0	73 (3.0)	13 (0.5)	1 (< 0.1)	0
Arthralgia	942 (37.3)	25 (1.0)	0	0	1058 (43.3)	31 (1.3)	0	0
Neutrophil count decreased	609 (24.1)	429 (17.0)	19 (0.8)	0	41 (1.7)	6 (0.2)	2 (0.1)	0
Nausea	588 (23.3)	6 (0.2)	0	0	190 (7.8)	1 (< 0.1)	0	0
Headache	575 (22.8)	11 (0.4)	0	0	415 (17.0)	4 (0.2)	0	0
Fatigue	564 (22.3)	19 (0.8)	0	0	322 (13.2)	4 (0.2)	0	0
COVID-19	537 (21.3)	18 (0.7)	0	3 (0.1)	345 (14.1)	11 (0.5)	0	1 (< 0.1)
SARS-CoV-2 test positive	532 (21.1)	0	0	0	332 (13.6)	0	0	0
Alanine aminotransferase increased	492 (19.5)	159 (6.3)	33 (1.3)	0	136 (5.6)	16 (0.7)	1 (< 0.1)	0
Hot flush	486 (19.2)	6 (0.2)	0	0	489 (20.0)	3 (0.1)	0	0
Asthenia	428 (17.0)	14 (0.6)	0	0	291 (11.9)	3 (0.1)	0	0
Aspartate aminotransferase increased	426 (16.9)	100 (4.0)	18 (0.7)	0	139 (5.7)	13 (0.5)	0	0
Alopecia	380 (15.0)	0	0	0	109 (4.5)	0	0	0
Diarrhoea	366 (14.5)	16 (0.6)	0	0	135 (5.5)	3 (0.1)	0	0
Leukopenia	337 (13.3)	94 (3.7)	0	0	50 (2.0)	2 (0.1)	0	0
Constipation	335 (13.3)	5 (0.2)	0	0	123 (5.0)	0	0	0
Cough	332 (13.1)	3 (0.1)	0	0	201 (8.2)	2 (0.1)	0	0
Insomnia	292 (11.6)	1 (< 0.1)	0	0	281 (11.5)	6 (0.2)	0	0
Pyrexia	280 (11.1)	5 (0.2)	0	0	147 (6.0)	2 (0.1)	0	0
Back pain	272 (10.8)	5 (0.2)	0	0	247 (10.1)	2 (0.1)	0	0
Pain in extremity	261 (10.3)	3 (0.1)	0	0	219 (9.0)	1 (< 0.1)	0	0
White blood cell count decreased	246 (9.7)	93 (3.7)	1 (< 0.1)	0	38 (1.6)	5 (0.2)	1 (< 0.1)	0
Dizziness	225 (8.9)	5 (0.2)	0	0	112 (4.6)	2 (0.1)	0	0
Hypertension	212 (8.4)	54 (2.1)	0	0	185 (7.6)	59 (2.4)	0	0

	Ribociclib plus ET // N=2525				ET only // N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Anaemia	211 (8.4)	8 (0.3)	0	0	73 (3.0)	6 (0.2)	1 (< 0.1)	0
Rash	202 (8.0)	4 (0.2)	0	0	69 (2.8)	3 (0.1)	0	0
Myalgia	199 (7.9)	2 (0.1)	0	0	182 (7.5)	8 (0.3)	0	0
Vomiting	198 (7.8)	10 (0.4)	0	0	96 (3.9)	1 (< 0.1)	0	0
Pruritus	188 (7.4)	2 (0.1)	0	0	77 (3.2)	1 (< 0.1)	0	0
Lymphoedema	170 (6.7)	4 (0.2)	0	0	186 (7.6)	3 (0.1)	0	0
Dyspnoea	166 (6.6)	13 (0.5)	0	0	102 (4.2)	10 (0.4)	0	0
Urinary tract infection	164 (6.5)	10 (0.4)	0	0	125 (5.1)	5 (0.2)	0	0
Abdominal pain	159 (6.3)	9 (0.4)	0	0	100 (4.1)	8 (0.3)	0	0
Hypomagnesaemia	155 (6.1)	0	1 (< 0.1)	0	39 (1.6)	0	0	0
Oropharyngeal pain	154 (6.1)	0	0	0	81 (3.3)	0	0	0
SARS-CoV-2 test negative	146 (5.8)	0	0	0	82 (3.4)	0	0	0
Anxiety	145 (5.7)	2 (0.1)	0	0	125 (5.1)	1 (< 0.1)	0	0
Nasopharyngitis	139 (5.5)	0	0	0	94 (3.8)	0	0	0
Abdominal pain upper	137 (5.4)	3 (0.1)	0	0	85 (3.5)	1 (< 0.1)	0	0
Oedema peripheral	136 (5.4)	1 (< 0.1)	0	0	77 (3.2)	0	0	0
Upper respiratory tract infection	123 (4.9)	2 (0.1)	0	0	63 (2.6)	0	0	0
Decreased appetite	120 (4.8)	1 (< 0.1)	0	0	47 (1.9)	0	0	0
Gamma-glutamyltransferase increased	119 (4.7)	23 (0.9)	3 (0.1)	0	67 (2.7)	22 (0.9)	0	0
Dyspepsia	118 (4.7)	0	0	0	73 (3.0)	0	0	0
Depression	116 (4.6)	5 (0.2)	0	0	101 (4.1)	4 (0.2)	2 (0.1)	0
Hyperkalaemia	114 (4.5)	3 (0.1)	0	0	26 (1.1)	2 (0.1)	0	0
Thrombocytopenia	110 (4.4)	5 (0.2)	0	0	45 (1.8)	0	1 (< 0.1)	0
Hypocalcaemia	110 (4.4)	1 (< 0.1)	0	0	14 (0.6)	0	0	0
Electrocardiogram QT prolonged	109 (4.3)	7 (0.3)	0	0	18 (0.7)	1 (< 0.1)	0	0
Breast pain	109 (4.3)	2 (0.1)	0	0	125 (5.1)	2 (0.1)	0	0
Vulvovaginal dryness	107 (4.2)	1 (< 0.1)	0	0	134 (5.5)	5 (0.2)	0	0

	Ribociclib plus ET // N=2525				ET only // N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hypokalaemia	104 (4.1)	8 (0.3)	0	0	35 (1.4)	7 (0.3)	0	0
Bone pain	104 (4.1)	5 (0.2)	0	0	104 (4.3)	2 (0.1)	0	0
Dry mouth	102 (4.0)	0	0	0	58 (2.4)	0	0	0
Influenza like illness	101 (4.0)	0	0	0	43 (1.8)	0	0	0
Blood creatinine increased	98 (3.9)	3 (0.1)	0	0	22 (0.9)	0	0	0
Dry eye	96 (3.8)	0	0	0	37 (1.5)	0	0	0
Musculoskeletal pain	93 (3.7)	0	0	0	85 (3.5)	2 (0.1)	0	0
Dry skin	91 (3.6)	0	0	0	31 (1.3)	0	0	0
Hyperglycaemia	88 (3.5)	4 (0.2)	0	0	76 (3.1)	4 (0.2)	0	0
Muscle spasms	87 (3.4)	1 (< 0.1)	0	0	62 (2.5)	0	0	0
Palpitations	87 (3.4)	0	0	0	37 (1.5)	0	0	0
Gastrooesophageal reflux disease	85 (3.4)	1 (< 0.1)	0	0	52 (2.1)	0	0	0
Stomatitis	84 (3.3)	0	0	0	16 (0.7)	0	0	0
Weight increased	81 (3.2)	11 (0.4)	0	0	69 (2.8)	5 (0.2)	0	0
Mucosal inflammation	81 (3.2)	2 (0.1)	0	0	9 (0.4)	0	0	0
Musculoskeletal chest pain	81 (3.2)	1 (< 0.1)	0	0	75 (3.1)	1 (< 0.1)	0	0
Blood magnesium decreased	80 (3.2)	1 (< 0.1)	0	0	31 (1.3)	0	0	0
Pain	77 (3.0)	3 (0.1)	0	0	53 (2.2)	3 (0.1)	0	0
Blood alkaline phosphatase increased	76 (3.0)	2 (0.1)	0	0	62 (2.5)	2 (0.1)	0	0
Osteopenia	76 (3.0)	0	0	0	76 (3.1)	1 (< 0.1)	0	0
Rhinorrhoea	73 (2.9)	0	0	0	27 (1.1)	0	0	0
Vertigo	72 (2.9)	2 (0.1)	0	0	43 (1.8)	2 (0.1)	0	0
Osteoporosis	71 (2.8)	3 (0.1)	0	0	91 (3.7)	0	0	0
Neck pain	71 (2.8)	0	0	0	47 (1.9)	1 (< 0.1)	0	0
Lacrimation increased	71 (2.8)	0	0	0	15 (0.6)	0	0	0
Lymphopenia	69 (2.7)	11 (0.4)	1 (< 0.1)	0	16 (0.7)	0	0	0
Sinusitis	67 (2.7)	0	0	0	41 (1.7)	0	0	0
	Ribociclib plus ET // N=2525				ET only // N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood bilirubin increased	66 (2.6)	4 (0.2)	1 (< 0.1)	0	28 (1.1)	1 (< 0.1)	0	0
Paraesthesia	65 (2.6)	0	0	0	57 (2.3)	0	0	0
Joint stiffness	64 (2.5)	1 (< 0.1)	0	0	70 (2.9)	0	0	0
Procedural pain	64 (2.5)	0	0	0	65 (2.7)	0	0	0
Herpes zoster	62 (2.5)	3 (0.1)	0	0	53 (2.2)	2 (0.1)	0	0
Lymphocyte count decreased	60 (2.4)	17 (0.7)	2 (0.1)	0	24 (1.0)	2 (0.1)	0	0
Lipase increased	58 (2.3)	18 (0.7)	7 (0.3)	0	33 (1.4)	6 (0.2)	6 (0.2)	0
Chest pain	58 (2.3)	1 (< 0.1)	0	0	50 (2.0)	3 (0.1)	0	0
Weight decreased	58 (2.3)	1 (< 0.1)	0	0	40 (1.6)	2 (0.1)	0	0
Nasal congestion	58 (2.3)	0	0	0	26 (1.1)	0	0	0
Non-cardiac chest pain	57 (2.3)	2 (0.1)	0	0	28 (1.1)	2 (0.1)	0	0
Blood lactate dehydrogenase increased	55 (2.2)	0	1 (< 0.1)	0	33 (1.4)	0	0	0
Neuropathy peripheral	54 (2.1)	0	1 (< 0.1)	0	55 (2.3)	1 (< 0.1)	0	0
Dysgeusia	54 (2.1)	0	0	0	14 (0.6)	0	0	0
Osteoarthritis	53 (2.1)	5 (0.2)	0	0	49 (2.0)	5 (0.2)	0	0
Platelet count decreased	53 (2.1)	1 (< 0.1)	0	0	11 (0.5)	2 (0.1)	0	0
Peripheral swelling	53 (2.1)	0	0	0	48 (2.0)	0	0	0
Axillary pain	52 (2.1)	0	0	0	37 (1.5)	1 (< 0.1)	0	0

Preferred terms are sorted in descending frequency based on frequency in ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.

Adverse events where a higher proportion of ribociclib plus ET-treated patients reported events, all grades, with a ≥ 10% relative difference to the ET only group, included:

Neutropenia: +38.5%; Decreased neutrophil count: +22.4%; Nausea: +15.5%; ALT increased: +13.9%; Leukopenia: +11.3%; AST increased: +11.2%; Alopecia: +10.6% and Arthralgia (43.3%). Hot flush (20.0%) were the only PTs reported in ≥ 20% of patients in the ET only group.

The number of patients reported with COVID-19 (21.3% vs. 14.1%) or a positive SARS-CoV-2 test (21.1% vs. 13.6%) was higher in the ribociclib plus ET group, compared with the ET only group.

2.5.3.2. Adverse events of grade 3-5 severity

Table 39. Common adverse events, grade ≥ 3, by preferred term and maximum grade (≥ 1% / either group), irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

	Ribociclib plus ET N=2525				ET only N=2442			
Preferred term	Grade ≥ 3 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade ≥ 3 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Total no. patients with at least 1 TEAE	**1607 (63.6)**	**1463 (57.9)**	**133 (5.3)**	**11 (0.4)**	**469 (19.2)**	**425 (17.4)**	**40 (1.6)**	**4 (0.2)**
Neutropenia	707 (28.0)	673 (26.7)	34 (1.3)	0	14 (0.6)	13 (0.5)	1 (< 0.1)	0
Neutrophil count decreased	448 (17.7)	429 (17.0)	19 (0.8)	0	8 (0.3)	6 (0.2)	2 (0.1)	0
Alanine aminotransferase increased	192 (7.6)	159 (6.3)	33 (1.3)	0	17 (0.7)	16 (0.7)	1 (< 0.1)	0
Aspartate aminotransferase increased	118 (4.7)	100 (4.0)	18 (0.7)	0	13 (0.5)	13 (0.5)	0	0
White blood cell count decreased	94 (3.7)	93 (3.7)	1 (< 0.1)	0	6 (0.2)	5 (0.2)	1 (< 0.1)	0
Leukopenia	94 (3.7)	94 (3.7)	0	0	2 (0.1)	2 (0.1)	0	0
Hypertension	54 (2.1)	54 (2.1)	0	0	59 (2.4)	59 (2.4)	0	0
Gamma-glutamyltransferase increased	26 (1.0)	23 (0.9)	3 (0.1)	0	22 (0.9)	22 (0.9)	0	0
Arthralgia	25 (1.0)	25 (1.0)	0	0	31 (1.3)	31 (1.3)	0	0

Preferred terms are sorted in descending frequency based on frequency in ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.

The most common grade ≥ 3 AEs in the ribociclib + ET arm were neutropenia (28.0%), neutrophil count decreased (17.7%), ALT increased (7.6%), AST increased 4.7%), WBC decreased (3.7%), and leukopenia (3.7%).

Grade 3 AEs were reported in 57.9% of patients in the ribociclib + ET group (mainly neutropenia, neutrophil count decreased, and ALT increased) and 17.4% of patients in the ET only group.

Grade 4 AEs were reported in 5.3% of patients in the ribociclib + ET group and 1.6% of patients in the ET only group. Neutropenia (1.3%) and ALT increased (1.3%) were the most frequently reported grade 4 AE (with incidences ≥ 1.0%) in the ribociclib + ET group.

In 11 patients (0.4%) a grade 5 event (AE with fatal outcome) were reported in the ribociclib + ET group. Amongst causes were cardiac arrest, cardiogenic shock, concurrent brain oedema and epilepsy, pneumonia, pulmonary embolism, and road traffic accident.

2.5.3.3. Adverse events suspected to be study treatment related

Overall, 93.8% of patients treated in the ribociclib + ET group had AEs suspected to be study treatment related.

2.5.3.4. Adverse drug reactions

Methodology for selection of ADRs

ADR candidates include two types of events namely 'pre-qualified candidate ADRs' and 'other candidate ADRs' identified through numerical screening rule. Ribociclib ADRs identified in advanced mBC were considered as 'pre-qualified candidate ADRs' for the adjuvant eBC setting.

'Other ADR candidates' are events for which a higher incidence versus comparator in the O12301C clinical database is observed. These have be identified using a numerical screening rule, i.e. algorithmically, based on all treatment emergent AEs.

ADR screening selection in the O12301C clinical database following the strategy, as follows:

1. Any AE (MedDRA PT) with ≥2% difference in AE incidence between ET + ribociclib vs ET only.

2. Any AE (MedDRA PT) with ≥5% incidence in ET + ribociclib group.

3. Any AE (MedDRA PT) from MedDRA SMQ (as per approved SMQs in RMP) with ≥2% in ET + ribociclib group.

4. Any AE (MedDRA PT) from SMQ (as per approved SMQs in RMP) with ≥5% difference in AE incidences between ET + ribociclib vs ET only.

5. Any Grade ≥3 AE with an absolute frequency ≥2 with no reports or lower reports on ET only group.

6. AEs and SAEs leading to discontinuation of ribociclib if occurrence at least 0.5% in ET + ribociclib group for Study O12301C.

7. Laboratory abnormalities with ≥5% difference in incidence between ET + ribociclib vs ET only.

In addition, the MAH´s safety database has been included in the screening for ADR candidates and has been used as an internal control against the clinical database. The purpose of this internal control is to identify those reported AEs that have not been identified in the clinical database before (ADR candidates arising from the MAH´s safety database only).

Identification of ADRs for ribociclib that considered the safety information from Study O12301C was performed based on the MAH´s 3-step process:

(1) selection of pre-qualified ADR candidates based on prior evidence of causality;

(2) statistical screening of the pivotal clinical study data for ADRs;

(3) medical evaluation of ADR candidates identified during Step 1 and/or Step 2.

To abridge the DCO of 11-Jan-2023, the ADR selection process included MedDRA Version 26.0 and eCRS as of 25-May-2023. As all other safety analyses being described in the SCS for Study O12301C were based on MedDRA Version 25.1 and eCRS as of 16-Dec-2022, coding changes between versions are detailed in SCS Study O12301C Appendix 2-Listing 14.6-1.2.

Summary of adverse drug reactions

Table 40***.*** Adverse drug reactions reported in the phase III clinical studies and during post-marketing experience

ET + Ribociclib N=2525
ET Only N=2442

Adverse drug reaction	Preferred term	SAE n (%)	Grade >=3 n (%)	Frequency n (%)	Freq. category	SAE n (%)	Grade >=3 n (%)	Frequency n (%)	Freq. category
Neutropenia	Total	1 (<0.1)	1113 (44.1)	1577 (62.5)	Very common	0	22 (0.9)	113 (4.6)	Common
	Neutropenia	0	707 (28.0)	1047 (41.5)		0	14 (0.6)	73 (3.0)	
	Neutrophil count decreased	1 (<0.1)	448 (17.7)	609 (24.1)		0	8 (0.3)	41 (1.7)	
	Granulocytopenia	0	0	4 (0.2)		0	0	0	
Infections	Total	42 (1.7)	49 (1.9)	917 (36.3)	Very common	26 (1.1)	23 (0.9)	642 (26.3)	Very common
	COVID-19	20 (0.8)	21 (0.8)	537 (21.3)		13 (0.5)	12 (0.5)	345 (14.1)	
	Urinary tract infection	6 (0.2)	10 (0.4)	164 (6.5)		3 (0.1)	5 (0.2)	125 (5.1)	
	Nasopharyngitis	0	0	139 (5.5)		0	0	94 (3.8)	

	Upper respiratory tract infection	1 (<0.1)	2 (0.1)	123 (4.9)		0	0	63 (2.6)	
	Sinusitis	0	0	67 (2.7)		0	0	41 (1.7)	
	Pneumonia	14 (0.6)	12 (0.5)	40 (1.6)		9 (0.4)	8 (0.3)	22 (0.9)	
	Bronchitis	1 (<0.1)	1 (<0.1)	34 (1.3)		1 (<0.1)	0	31 (1.3)	
	Cystitis	0	0	34 (1.3)		1 (<0.1)	0	26 (1.1)	
	Pharyngitis	0	0	23 (0.9)		0	0	23 (0.9)	
	Respiratory tract infection	0	0	23 (0.9)		1 (<0.1)	1 (<0.1)	18 (0.7)	
	Rhinitis	0	0	23 (0.9)		0	0	16 (0.7)	
	Lower respiratory tract infection	0	1 (<0.1)	11 (0.4)		0	0	12 (0.5)	
	Tracheitis	0	0	10 (0.4)		0	0	8 (0.3)	
	Viral upper respiratory tract infection	1 (<0.1)	1 (<0.1)	8 (0.3)		0	0	1 (<0.1)	
	Laryngitis	0	0	6 (0.2)		0	0	8 (0.3)	
	Acute sinusitis	0	0	3 (0.1)		0	0	1 (<0.1)	
	Urosepsis	3 (0.1)	3 (0.1)	3 (0.1)		1 (<0.1)	1 (<0.1)	1 (<0.1)	
	Escherichia urinary tract infection	1 (<0.1)	2 (0.1)	2 (0.1)		0	0	0	
	Atypical pneumonia	0	0	1 (<0.1)		0	0	0	
	Viral sinusitis	0	0	1 (<0.1)		0	0	0	
Nausea	Total	2 (0.1)	6 (0.2)	588 (23.3)	Very common	1 (<0.1)	1 (<0.1)	190 (7.8)	Common
	Nausea	2 (0.1)	6 (0.2)	588 (23.3)		1 (<0.1)	1 (<0.1)	190 (7.8)	
Headache	Total	0	11 (0.4)	580 (23.0)	Very common	2 (0.1)	4 (0.2)	417 (17.1)	Very common
	Headache	0	11 (0.4)	575 (22.8)		2 (0.1)	4 (0.2)	415 (17.0)	
	Tension headache	0	0	7 (0.3)		0	0	4 (0.2)	
Fatigue	Total	1 (<0.1)	19 (0.8)	564 (22.3)	Very common	0	4 (0.2)	322 (13.2)	Very common
	Fatigue	1 (<0.1)	19 (0.8)	564 (22.3)		0	4 (0.2)	322 (13.2)	
Leukopenia	Total	0	184 (7.3)	564 (22.3)	Very common	0	8 (0.3)	88 (3.6)	Common
	Leukopenia	0	94 (3.7)	337 (13.3)		0	2 (0.1)	50 (2.0)	
	White blood cell count decreased	0	94 (3.7)	246 (9.7)		0	6 (0.2)	38 (1.6)	
Abnormal liver function tests	Total	9 (0.4)	197 (7.8)	563 (22.3)	Very common	0	25 (1.0)	186 (7.6)	Common
	Alanine aminotransferase increased	9 (0.4)	192 (7.6)	492 (19.5)		0	17 (0.7)	136 (5.6)	

	Aspartate aminotransferase increased	5 (0.2)	118 (4.7)	426 (16.9)		0	13 (0.5)	139 (5.7)	
	Blood bilirubin increased	0	5 (0.2)	66 (2.6)		0	1 (<0.1)	28 (1.1)	
Asthenia	Total	1 (<0.1)	14 (0.6)	428 (17.0)	Very common	1 (<0.1)	3 (0.1)	291 (11.9)	Very common
	Asthenia	1 (<0.1)	14 (0.6)	428 (17.0)		1 (<0.1)	3 (0.1)	291 (11.9)	
Alopecia	Total	0	0	380 (15.0)	Very common	0	0	109 (4.5)	Common
	Alopecia	0	0	380 (15.0)		0	0	109 (4.5)	
Diarrhoea	Total	5 (0.2)	16 (0.6)	366 (14.5)	Very common	0	3 (0.1)	135 (5.5)	Common
	Diarrhoea	5 (0.2)	16 (0.6)	366 (14.5)		0	3 (0.1)	135 (5.5)	
Constipation	Total	3 (0.1)	5 (0.2)	335 (13.3)	Very common	0	0	123 (5.0)	Common
	Constipation	3 (0.1)	5 (0.2)	335 (13.3)		0	0	123 (5.0)	
Cough	Total	0	3 (0.1)	332 (13.1)	Very common	0	2 (0.1)	201 (8.2)	Common
	Cough	0	3 (0.1)	332 (13.1)		0	2 (0.1)	201 (8.2)	
Pyrexia	Total	7 (0.3)	5 (0.2)	280 (11.1)	Very common	1 (<0.1)	2 (0.1)	147 (6.0)	Common
	Pyrexia	7 (0.3)	5 (0.2)	280 (11.1)		1 (<0.1)	2 (0.1)	147 (6.0)	
Abdominal pain	Total	1 (<0.1)	12 (0.5)	277 (11.0)	Very common	4 (0.2)	9 (0.4)	179 (7.3)	Common
	Abdominal pain	1 (<0.1)	9 (0.4)	159 (6.3)		3 (0.1)	8 (0.3)	100 (4.1)	
	Abdominal pain upper	0	3 (0.1)	137 (5.4)		1 (<0.1)	1 (<0.1)	85 (3.5)	
Rash	Total	0	4 (0.2)	233 (9.2)	Common	0	3 (0.1)	85 (3.5)	Common
	Rash	0	4 (0.2)	202 (8.0)		0	3 (0.1)	69 (2.8)	
	Rash maculo-papular	0	0	27 (1.1)		0	0	9 (0.4)	
	Rash pruritic	0	0	16 (0.6)		0	0	8 (0.3)	
Dizziness	Total	2 (0.1)	5 (0.2)	225 (8.9)	Common	1 (<0.1)	2 (0.1)	112 (4.6)	Common
	Dizziness	2 (0.1)	5 (0.2)	225 (8.9)		1 (<0.1)	2 (0.1)	112 (4.6)	
Anaemia	Total	3 (0.1)	8 (0.3)	215 (8.5)	Common	2 (0.1)	7 (0.3)	75 (3.1)	Common
	Anaemia	3 (0.1)	8 (0.3)	211 (8.4)		2 (0.1)	7 (0.3)	73 (3.0)	
	Haemoglobin decreased	0	0	3 (0.1)		0	0	1 (<0.1)	
	Microcytic anaemia	0	0	1 (<0.1)		0	0	1 (<0.1)	
	Haematocrit decreased	0	0	1 (<0.1)		0	0	0	
Vomiting	Total	2 (0.1)	10 (0.4)	198 (7.8)	Common	1 (<0.1)	1 (<0.1)	96 (3.9)	Common
	Vomiting	2 (0.1)	10 (0.4)	198 (7.8)		1 (<0.1)	1 (<0.1)	96 (3.9)	

Pruritus	Total	0	2 (0.1)	188 (7.4)	Common	0	1 (<0.1)	77 (3.2)	Common
	Pruritus	0	2 (0.1)	188 (7.4)		0	1 (<0.1)	77 (3.2)	
Peripheral oedema	Total	0	1 (<0.1)	183 (7.2)	Common	0	0	121 (5.0)	Common
	Oedema peripheral	0	1 (<0.1)	136 (5.4)		0	0	77 (3.2)	
	Peripheral swelling	0	0	53 (2.1)		0	0	48 (2.0)	
Dyspnoea	Total	12 (0.5)	13 (0.5)	166 (6.6)	Common	5 (0.2)	10 (0.4)	102 (4.2)	Common
	Dyspnoea	12 (0.5)	13 (0.5)	166 (6.6)		5 (0.2)	10 (0.4)	102 (4.2)	
Thrombocytopenia	Total	0	6 (0.2)	162 (6.4)	Common	0	3 (0.1)	56 (2.3)	Common
	Thrombocytopenia	0	5 (0.2)	110 (4.4)		0	1 (<0.1)	45 (1.8)	
	Platelet count decreased	0	1 (<0.1)	53 (2.1)		0	2 (0.1)	11 (0.5)	
Oropharyngeal pain	Total	0	0	154 (6.1)	Common	0	0	81 (3.3)	Common
	Oropharyngeal pain	0	0	154 (6.1)		0	0	81 (3.3)	
Stomatitis	Total	0	2 (0.1)	154 (6.1)	Common	0	0	24 (1.0)	Uncommon
	Stomatitis	0	0	84 (3.3)		0	0	16 (0.7)	
	Mucosal inflammation	0	2 (0.1)	81 (3.2)		0	0	9 (0.4)	
Hypocalcaemia	Total	0	1 (<0.1)	134 (5.3)	Common	1 (<0.1)	0	26 (1.1)	Common
	Hypocalcaemia	0	1 (<0.1)	110 (4.4)		1 (<0.1)	0	14 (0.6)	
	Blood calcium decreased	0	0	30 (1.2)		0	0	13 (0.5)	
Lymphopenia	Total	0	30 (1.2)	124 (4.9)	Common	0	2 (0.1)	39 (1.6)	Common
	Lymphopenia	0	12 (0.5)	69 (2.7)		0	0	16 (0.7)	
	Lymphocyte count decreased	0	19 (0.8)	60 (2.4)		0	2 (0.1)	24 (1.0)	
Hypokalaemia	Total	3 (0.1)	8 (0.3)	121 (4.8)	Common	0	7 (0.3)	41 (1.7)	Common
	Hypokalaemia	3 (0.1)	8 (0.3)	104 (4.1)		0	7 (0.3)	35 (1.4)	
	Blood potassium decreased	0	0	20 (0.8)		0	0	6 (0.2)	
Decreased apetite	Total	0	1 (<0.1)	120 (4.8)	Common	0	0	47 (1.9)	Common
	Decreased appetite	0	1 (<0.1)	120 (4.8)		0	0	47 (1.9)	
Electrocardiogram prolonged	Total	0	7 (0.3)	109 (4.3)	Common	0	1 (<0.1)	18 (0.7)	Uncommon
	Electrocardiogram QT prolonged	0	7 (0.3)	109 (4.3)		0	1 (<0.1)	18 (0.7)	
Blood creatinine increased	Total	1 (<0.1)	3 (0.1)	98 (3.9)	Common	0	0	22 (0.9)	Uncommon

	Blood creatinine increased	1 (<0.1)	3 (0.1)	98 (3.9)		0	0	22 (0.9)	
Hepatotoxicity	Total	13 (0.5)	16 (0.6)	36 (1.4)	Common	1 (<0.1)	1 (<0.1)	13 (0.5)	Uncommon
	Hepatotoxicity	5 (0.2)	7 (0.3)	15 (0.6)		0	0	1 (<0.1)	
	Hepatic cytolysis	1 (<0.1)	3 (0.1)	11 (0.4)		1 (<0.1)	1 (<0.1)	12 (0.5)	
	Drug-induced liver injury	6 (0.2)	5 (0.2)	9 (0.4)		0	0	0	
	Autoimmune hepatitis	1 (<0.1)	1 (<0.1)	1 (<0.1)		0	0	0	
Febrile neutropenia	Total	1 (<0.1)	7 (0.3)	7 (0.3)	Uncommon	0	0	0	
	Febrile neutropenia	1 (<0.1)	7 (0.3)	7 (0.3)		0	0	0	

Numbers (n) represent counts of subjects. MedDRA version 26.0, 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)

2.5.3.5. Adverse event of special interest (AESI)

Table 41. Adverse events of special interest by grouping, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

AESI grouping	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Myelosuppression AESI		
Neutropenia	1579 (62.5)	113 (4.6)
Leukopenia	595 (23.6)	111 (4.5)
Anemia	216 (8.6)	78 (3.2)
Thrombocytopenia	162 (6.4)	56 (2.3)
Other	0	1 (< 0.1)
Non-myelosuppression AESI		
Infections	1253 (49.6)	884 (36.2)
Hepatobiliary toxicity	667 (26.4)	273 (11.2)
Renal toxicity	152 (6.0)	58 (2.4)
QT interval prolongation	134 (5.3)	34 (1.4)
Second primary malignancies	48 (1.9)	49 (2.0)
ILD / Pneumonitis	39 (1.5)	22 (0.9)
Reproductive toxicity	32 (1.3)	27 (1.1)

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

2.5.3.5.1. Myelosuppressive AESIs

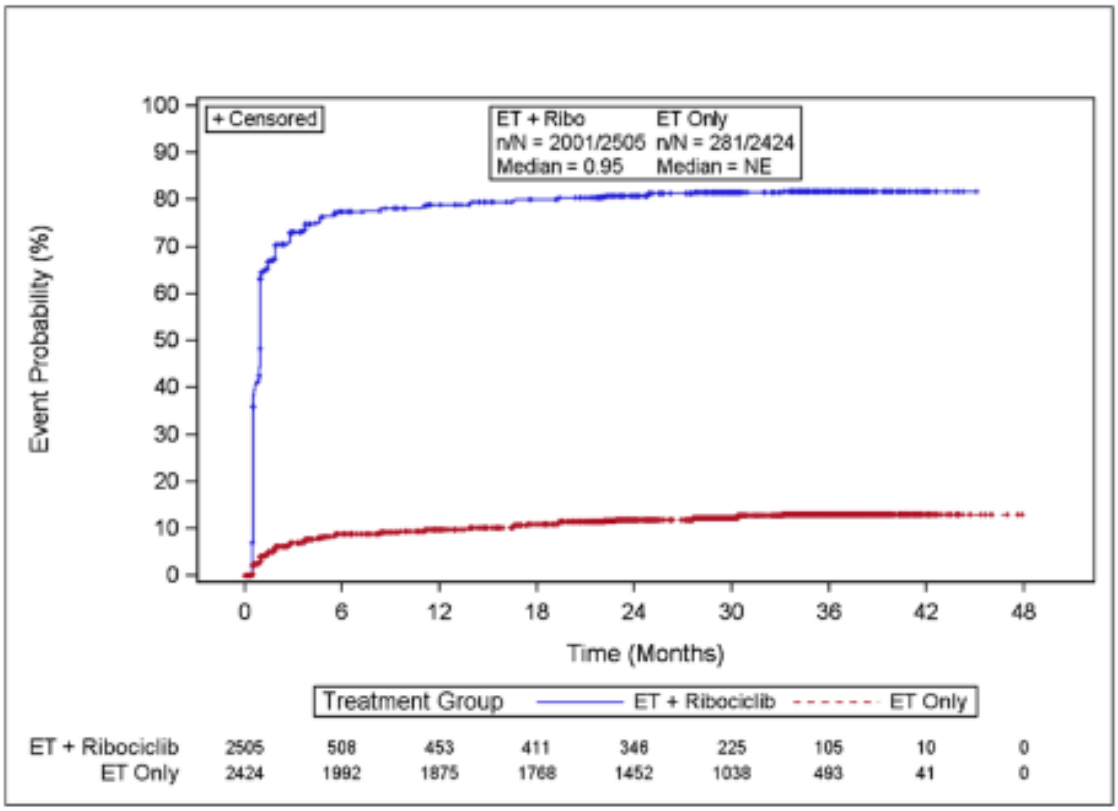
Neutropenia

Table 42. Clinical impact of Neutropenia AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Myelosuppression – Neutropenia Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**1579 (62.5)**	**113 (4.6)**
Neutropenia	1047 (41.5)	73 (3.0)
Neutrophil count decreased	609 (24.1)	41 (1.7)
Febrile neutropenia	7 (0.3)	0
Granulocytopenia	4 (0.2)	0
CTCAE grade ≥ 3 AEs	**1118 (44.3)**	**22 (0.9)**
Neutropenia	707 (28.0)	14 (0.6)
Neutrophil count decreased	448 (17.7)	8 (0.3)
Febrile neutropenia	7 (0.3)	0
SAEs	**2 (0.1)**	**0**
Febrile neutropenia	1 (< 0.1)	0
Neutrophil count decreased	1 (< 0.1)	0
AEs leading to discontinuation	**28 (1.1)**	**0**
Neutropenia	19 (0.8)	0
Neutrophil count decreased	7 (0.3)	0
Myelosuppression – Neutropenia **Preferred term**	**Ribociclib plus ET** **N=2525** **n (%)**	**ET only** **N=2442** **n (%)**
Febrile neutropenia	2 (0.1)	0
AEs leading to dose adjustment	**358 (14.2)**	**0**
Neutropenia	215 (8.5)	0
Neutrophil count decreased	141 (5.6)	0
Febrile neutropenia	2 (0.1)	0
AEs leading to dose interruption	**1093 (43.3)**	**3 (0.1)**
Neutropenia	683 (27.0)	1 (< 0.1)
Neutrophil count decreased	441 (17.5)	2 (0.1)
Febrile neutropenia	4 (0.2)	0

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Figure 14. Kaplan-Meier plot of neutropenia, grade 2 or higher, as time-to-first occurrence by treatment group in Study O12301C (Safety set based on cut-off date 11-Jan-2023)



Based on neutrophil counts.
N=total number of patients included in the analysis. Patients meeting the criteria for an event at baseline and patients with missing baseline are excluded from the analysis. n=number of patients with event. NE=not evaluable.

Table 43. Side-by-side comparison of Neutropenia AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Myelosupression – Neutropenia	**Ribociclib plus ET N=2524 n (%): 95% CI**	**ET only N=2444 n (%): 95% CI**	**Ribociclib + ET N=1065 n (%): 95% CI**	**PBO + ET N=818 n (%): 95% CI**
Total no. patients	**1568 (62.1): 60.2, 64.0**	**110 (4.5): 3.7, 5.4**	**806 (75.7): 73.0, 78.2**	**56 (6.8): 5.2, 8.8**
Grade ≥ 3	1106 (43.8): 41.9, 45.8	20 (0.8): 0.5, 1.3	666 (62.5): 59.5, 65.5	20 (2.4): 1.5, 3.8
SAEs	2 (0.1): 0.0, 0.3	0	26 (2.4): 1.6, 3.6	1 (0.1): 0.0, 0.7
AEs with fatal outcome	0	0	0	0
AEs leading to discontinuation	32 (1.3): 0.9, 1.8	0	11 (1.0): 0.5, 1.8	0
AEs leading to dose adjustment	317 (12.6): 11.3, 13.9	0	275 (25.8): 23.2, 28.6	2 (0.2): 0.0, 0.9
AEs leading to dose interruption	1080 (42.8): 40.8, 44.7	3 (0.1): 0.0, 0.4	605 (56.8): 53.8, 59.8	11 (1.3): 0.7, 2.4

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

Leukopenia

Table 44 Clinical impact of Leukopenia AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Myelosuppression – Leukopenia Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**595 (23.6)**	**111 (4.5)**
Leukopenia	337 (13.3)	50 (2.0)
White blood cell count decreased	246 (9.7)	38 (1.6)
Lymphopenia	69 (2.7)	16 (0.7)
Lymphocyte count decreased	60 (2.4)	24 (1.0)
CTCAE grade ≥ 3 AEs	**202 (8.0)**	**10 (0.4)**
Leukopenia	94 (3.7)	2 (0.1)
White blood cell count decreased	94 (3.7)	6 (0.2)
Lymphocyte count decreased	19 (0.8)	2 (0.1)
Lymphopenia	12 (0.5)	0
AEs leading to discontinuation	**6 (0.2)**	**0**
Leukopenia	2 (0.1)	0
White blood cell count decreased	2 (0.1)	0
Lymphocyte count decreased	1 (< 0.1)	0
Lymphopenia	1 (< 0.1)	0

Myelosuppression – Leukopenia Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
AEs leading to dose adjustment	**45 (1.8)**	**0**
White blood cell count decreased	26 (1.0)	0
Leukopenia	17 (0.7)	0
Lymphocyte count decreased	1 (< 0.1)	0
Lymphopenia	1 (< 0.1)	0
AEs leading to dose interruption	**160 (6.3)**	**0**
Leukopenia	81 (3.2)	0
White blood cell count decreased	70 (2.8)	0
Lymphocyte count decreased	12 (0.5)	0
Lymphopenia	7 (0.3)	0

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Table 45. Side-byside comparison of Leukopenia AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Myelosupression – Leukopenia	**Ribociclib plus ET N=2524 n (%): 95% CI**	**ET only N=2444 n (%): 95% CI**	**Ribociclib + ET N=1065 n (%): 95% CI**	**PBO + ET N=818 n (%): 95% CI**
Total no. patients	**583 (23.1): 21.5, 24.8**	**110 (4.5): 3.7, 5.4**	**372 (34.9) (32.1, 37.9)**	**38 (4.6) (3.3, 6.3)**
Grade ≥ 3	197 (7.8): 6.8, 8.9	9 (0.4): 0.2, 0.7	210 (19.7) (17.4, 22.2)	9 (1.1) (0.5, 2.1)
SAEs	0	0	3 (0.3) (0.1, 0.8)	0
AEs with fatal outcome	0	0	0	0
AEs leading to discontinuation	7 (0.3): 0.1, 0.6	0	1 (0.1) (0.0, 0.5)	0
AEs leading to dose adjustment	37 (1.5): 1.0, 2.0	0	26 (2.4) (1.6, 3.6)	0
AEs leading to dose interruption	155 (6.1): 5.2, 7.1	0	116 (10.9) (9.1, 12.9)	1 (0.1) (0.0, 0.7)

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

Anaemia

Table 46. Clinical impact of Anemia AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Myelosuppression – Anemia Preferred term	**Ribociclib plus ET N=2525 n (%)**	**ET only N=2442 n (%)**
All AEs	**216 (8.6)**	**78 (3.2)**
Anaemia	211 (8.4)	73 (3.0)
Haemoglobin decreased	3 (0.1)	1 (< 0.1)
Red blood cell count decreased	3 (0.1)	2 (0.1)
Haematocrit decreased	1 (< 0.1)	0
Microcytic anaemia	1 (< 0.1)	1 (< 0.1)
Normocytic anaemia	0	1 (< 0.1)
CTCAE grade ≥ 3 AEs	**8 (0.3)**	**8 (0.3)**
Anaemia	8 (0.3)	7 (0.3)
Red blood cell count decreased	0	1 (< 0.1)
SAEs	**3 (0.1)**	**3 (0.1)**
Anaemia	3 (0.1)	2 (0.1)
Red blood cell count decreased	0	1 (< 0.1)
AEs leading to discontinuation	**2 (0.1)**	**0**
Anaemia	2 (0.1)	0
Myelosuppression – Anemia Preferred term	**Ribociclib plus ET N=2525 n (%)**	**ET only N=2442 n (%)**
AEs leading to dose adjustment	**1 (< 0.1)**	**0**
Anaemia	1 (< 0.1)	0
AEs leading to dose interruption	**10 (0.4)**	**1 (< 0.1)**
Anaemia	10 (0.4)	1 (< 0.1)

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 28-Aug-2023.

Table 47. Side-by-side comparison of Anemia AESI by AE catergories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Myelosupression – Anemia	**Ribociclib plus ET N=2524 n (%): 95% CI**	**ET only N=2444 n (%): 95% CI**	**Ribociclib + ET N=1065 n (%): 95% CI**	**PBO + ET N=818 n (%): 95% CI**
Total no. patients	**209 (8.3): 7.2, 9.4**	**74 (3.0): 2.4, 3.8**	**228 (21.4): 19.0, 24.0**	**69 (8.4): 6.6, 10.6**
Grade ≥ 3	7 (0.3): 0.1, 0.6	6 (0.2): 0.1, 0.5	41 (3.8): 2.8, 5.2	18 (2.2): 1.3, 3.5
SAEs	3 (0.1): 0.0, 0.3	1 (< 0.1): 0.0, 0.2	12 (1.1): 0.6, 2.0	3 (0.4): 0.1, 1.1
AEs with fatal outcome	0	0	0	0
AEs leading to discontinuation	2 (0.1): 0.0, 0.3	0	0	0
AEs leading to dose adjustment	1 (< 0.1): 0.0, 0.2	0	5 (0.5): 0.2, 1.1	0
AEs leading to dose interruption	12 (0.5): 0.2, 0.8	1 (< 0.1): 0.0, 0.2	28 (2.6): 1.8, 3.8	7 (0.9): 0.3, 1.8

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

Thrombocytopenia

Table 48 Clinical impact of Thrombocytopenia AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Myelosuppression – Thrombocytopenia Preferred term	**Ribociclib plus ET N=2525 n (%)**	**ET only N=2442 n (%)**
All AEs	**162 (6.4)**	**56 (2.3)**
Thrombocytopenia	110 (4.4)	45 (1.8)
Platelet count decreased	53 (2.1)	11 (0.5)
CTCAE grade ≥ 3 AEs	**6 (0.2)**	**3 (0.1)**
Thrombocytopenia	5 (0.2)	1 (< 0.1)
Platelet count decreased	1 (< 0.1)	2 (0.1)
AEs leading to discontinuation	**1 (< 0.1)**	**0**
Thrombocytopenia	1 (< 0.1)	0
AEs leading to dose adjustment	**2 (0.1)**	**0**
Platelet count decreased	1 (< 0.1)	0
Thrombocytopenia	1 (< 0.1)	0
AEs leading to dose interruption	**20 (0.8)**	**1 (< 0.1)**
Thrombocytopenia	12 (0.5)	0
Platelet count decreased	9 (0.4)	1 (< 0.1)
Myelosuppression – Thrombocytopenia Preferred term	**Ribociclib plus ET N=2525 n (%)**	**ET only N=2442 n (%)**

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Table 49. Side-by-side comparison of Thrombocytopenia AESI by AE categories of Study O12301C vs. Pooled aBC (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Myelosupression – Thrombocytopenia	**Ribociclib plus ET N=2524 n (%): 95% CI**	**ET only N=2444 n (%): 95% CI**	**Ribociclib + ET N=1065 n (%): 95% CI**	**PBO + ET N=818 n (%): 95% CI**
Total no. patients	**161 (6.4): 5.5, 7.4**	**53 (2.2): 1.6, 2.8**	**105 (9.9): 8.1, 11.8**	**15 (1.8): 1.0, 3.0**
Grade ≥ 3	6 (0.2): 0.1, 0.5	3 (0.1): 0.0, 0.4	9 (0.8): 0.4, 1.6	2 (0.2): 0.0, 0.9
SAEs	0	0	5 (0.5): 0.2, 1.1	1 (0.1): 0.0, 0.7
AEs with fatal outcome	0	0	0	0
AEs leading to discontinuation	1 (< 0.1): 0.0, 0.2	0	0	1 (0.1): 0.0, 0.7
AEs leading to dose adjustment	2 (0.1): 0.0, 0.3	0	7 (0.7): 0.3, 1.3	0
AEs leading to dose interruption	20 (0.8): 0.5, 1.2	1 (< 0.1): 0.0, 0.2	17 (1.6): 0.9, 2.5	0

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

2.5.3.5.2. Non-myelosuppressive AESI

Infections

Clinical impact of Infections AESI by preferred term, irrespective of causality (⩾ 3 patients / either group) (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Infections Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**1253 (49.6)**	**884 (36.2)**
COVID-19	537 (21.3)	345 (14.1)
Urinary tract infection	164 (6.5)	125 (5.1)
Nasopharyngitis	139 (5.5)	94 (3.8)
Upper respiratory tract infection	123 (4.9)	63 (2.6)
Sinusitis	67 (2.7)	41 (1.7)
Herpes zoster	62 (2.5)	53 (2.2)
Suspected COVID-19	47 (1.9)	24 (1.0)
Pneumonia	40 (1.6)	22 (0.9)
Oral herpes	37 (1.5)	13 (0.5)
Cellulitis	35 (1.4)	18 (0.7)
Bronchitis	34 (1.3)	31 (1.3)
Cystitis	34 (1.3)	26 (1.1)
Influenza	34 (1.3)	22 (0.9)
Gastroenteritis	31 (1.2)	19 (0.8)
Respiratory tract infection viral	30 (1.2)	29 (1.2)
Tooth infection	30 (1.2)	19 (0.8)
Conjunctivitis	29 (1.1)	13 (0.5)
Mastitis	27 (1.1)	19 (0.8)
Pharyngitis	23 (0.9)	23 (0.9)
Respiratory tract infection	23 (0.9)	18 (0.7)
Rhinitis	23 (0.9)	16 (0.7)
Ear infection	19 (0.8)	13 (0.5)
Skin infection	19 (0.8)	15 (0.6)
Pneumonia viral	16 (0.6)	7 (0.3)
Breast cellulitis	15 (0.6)	5 (0.2)

Infections Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Gastroenteritis viral	15 (0.6)	9 (0.4)
Chronic gastritis	14 (0.6)	7 (0.3)
Tonsillitis	13 (0.5)	8 (0.3)
COVID-19 pneumonia	12 (0.5)	7 (0.3)
Erysipelas	12 (0.5)	9 (0.4)
Fungal infection	12 (0.5)	10 (0.4)
Hordeolum	12 (0.5)	4 (0.2)
Periodontitis	12 (0.5)	4 (0.2)
Postoperative wound infection	12 (0.5)	5 (0.2)
Gingivitis	11 (0.4)	4 (0.2)
Lower respiratory tract infection	11 (0.4)	12 (0.5)
Tooth abscess	11 (0.4)	4 (0.2)
Wound infection	11 (0.4)	5 (0.2)
Oral candidiasis	10 (0.4)	5 (0.2)
Tracheitis	10 (0.4)	8 (0.3)
Viral infection	10 (0.4)	11 (0.5)
Diverticulitis	9 (0.4)	7 (0.3)
Eye infection	9 (0.4)	5 (0.2)
Pulpitis dental	9 (0.4)	2 (0.1)
Pyelonephritis	9 (0.4)	4 (0.2)
Vulvovaginal candidiasis	9 (0.4)	5 (0.2)
Food poisoning	8 (0.3)	3 (0.1)
Gastrointestinal infection	8 (0.3)	3 (0.1)
Localised infection	8 (0.3)	5 (0.2)
Viral upper respiratory tract infection	8 (0.3)	1 (< 0.1)
Candida infection	7 (0.3)	4 (0.2)
Herpes simplex	7 (0.3)	3 (0.1)
Vaginal infection	7 (0.3)	13 (0.5)
Vulvovaginal mycotic infection	7 (0.3)	2 (0.1)
Acarodermatitis	6 (0.2)	0
Laryngitis	6 (0.2)	8 (0.3)
Onychomycosis	6 (0.2)	5 (0.2)
Oral infection	6 (0.2)	0
Paronychia	6 (0.2)	4 (0.2)
Device related infection	5 (0.2)	5 (0.2)
Helicobacter infection	5 (0.2)	5 (0.2)
Post procedural infection	5 (0.2)	6 (0.2)
Rash pustular	5 (0.2)	1 (< 0.1)
Tinea pedis	5 (0.2)	1 (< 0.1)
Appendicitis	4 (0.2)	3 (0.1)
Bacteraemia	4 (0.2)	0
Furuncle	4 (0.2)	2 (0.1)
Herpes virus infection	4 (0.2)	1 (< 0.1)
Infected bite	4 (0.2)	0

Infections Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Infected seroma	4 (0.2)	1 (< 0.1)
Pyelonephritis chronic	4 (0.2)	4 (0.2)
Skin papilloma	4 (0.2)	4 (0.2)
Acute sinusitis	3 (0.1)	1 (< 0.1)
Bacterial vaginosis	3 (0.1)	3 (0.1)
Carbuncle	3 (0.1)	0
Coronavirus infection	3 (0.1)	2 (0.1)
Folliculitis	3 (0.1)	3 (0.1)
Fungal skin infection	3 (0.1)	7 (0.3)
Herpes simplex reactivation	3 (0.1)	1 (< 0.1)
Infected cyst	3 (0.1)	1 (< 0.1)
Labyrinthitis	3 (0.1)	3 (0.1)
Nasal herpes	3 (0.1)	0
Otitis externa	3 (0.1)	2 (0.1)
Post procedural cellulitis	3 (0.1)	0
Pustule	3 (0.1)	0
Pyelonephritis acute	3 (0.1)	0
Sialoadenitis	3 (0.1)	1 (< 0.1)
Urosepsis	3 (0.1)	1 (< 0.1)
Breast abscess	2 (0.1)	3 (0.1)
Lymphangitis	2 (0.1)	3 (0.1)
Oral fungal infection	2 (0.1)	4 (0.2)
Subcutaneous abscess	2 (0.1)	5 (0.2)
Pharyngotonsillitis	1 (< 0.1)	3 (0.1)
Sepsis	1 (< 0.1)	3 (0.1)
Vestibular neuronitis	1 (< 0.1)	3 (0.1)
Cervicitis	0	4 (0.2)
CTCAE grade ≥ 3 AEs	**138 (5.5)**	**77 (3.2)**
COVID-19	21 (0.8)	12 (0.5)
Pneumonia	12 (0.5)	8 (0.3)
Cellulitis	11 (0.4)	8 (0.3)
Urinary tract infection	10 (0.4)	5 (0.2)
Breast cellulitis	9 (0.4)	3 (0.1)
COVID-19 pneumonia	9 (0.4)	5 (0.2)
Mastitis	7 (0.3)	5 (0.2)
Postoperative wound infection	5 (0.2)	2 (0.1)
Appendicitis	4 (0.2)	3 (0.1)
Pyelonephritis	4 (0.2)	2 (0.1)
Bacteraemia	3 (0.1)	0
Device related infection	3 (0.1)	5 (0.2)
Herpes zoster	3 (0.1)	2 (0.1)
Urosepsis	3 (0.1)	1 (< 0.1)
Wound infection	3 (0.1)	3 (0.1)
Erysipelas	2 (0.1)	3 (0.1)

Infections Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Post procedural infection	2 (0.1)	3 (0.1)
Sepsis	1 (< 0.1)	3 (0.1)
SAEs	**126 (5.0)**	**73 (3.0)**
COVID-19	20 (0.8)	13 (0.5)
Pneumonia	14 (0.6)	9 (0.4)
Breast cellulitis	9 (0.4)	3 (0.1)
COVID-19 pneumonia	9 (0.4)	5 (0.2)
Cellulitis	7 (0.3)	6 (0.2)
Urinary tract infection	6 (0.2)	3 (0.1)
Postoperative wound infection	5 (0.2)	2 (0.1)
Appendicitis	4 (0.2)	2 (0.1)
Erysipelas	4 (0.2)	3 (0.1)
Mastitis	4 (0.2)	2 (0.1)
Pneumonia viral	4 (0.2)	3 (0.1)
Suspected COVID-19	4 (0.2)	1 (< 0.1)
Bacteraemia	3 (0.1)	0
Pyelonephritis	3 (0.1)	2 (0.1)
Urosepsis	3 (0.1)	1 (< 0.1)
Device related infection	2 (0.1)	3 (0.1)
Post procedural infection	2 (0.1)	3 (0.1)
Sepsis	1 (< 0.1)	3 (0.1)
AEs leading to discontinuation	**20 (0.8)**	**3 (0.1)**
COVID-19	8 (0.3)	1 (< 0.1)
AEs leading to dose adjustment	**11 (0.4)**	**0**
AEs leading to dose interruption	**455 (18.0)**	**35 (1.4)**
COVID-19	228 (9.0)	20 (0.8)
Upper respiratory tract infection	27 (1.1)	1 (< 0.1)
Nasopharyngitis	26 (1.0)	1 (< 0.1)
Herpes zoster	20 (0.8)	0
Cellulitis	18 (0.7)	0
Suspected COVID-19	14 (0.6)	4 (0.2)
Urinary tract infection	14 (0.6)	0
Influenza	13 (0.5)	0
Mastitis	12 (0.5)	1 (< 0.1)
Pneumonia	12 (0.5)	0
Gastroenteritis	11 (0.4)	1 (< 0.1)
Breast cellulitis	10 (0.4)	0
Postoperative wound infection	8 (0.3)	0
Tooth infection	8 (0.3)	0
COVID-19 pneumonia	7 (0.3)	2 (0.1)
Erysipelas	7 (0.3)	1 (< 0.1)
Sinusitis	7 (0.3)	0
Gastroenteritis viral	6 (0.2)	0
Viral upper respiratory tract infection	5 (0.2)	0

Table 50. Side-by-side comparison of Infections AESI by AE catergories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Infections	Ribociclib plus ET N=2524 n (%): 95% CI	ET only N=2444 n (%): 95% CI	Ribociclib + ET N=1065 n (%): 95% CI	PBO + ET N=818 n (%): 95% CI
Total no. patients	**1199 (47.5): 45.5, 49.5**	**836 (34.2): 32.3, 36.1**	**624 (58.6): 55.6, 61.6**	**388 (47.4): 44.0, 50.9**
Grade ≥ 3	131 (5.2): 4.4, 6.1	72 (2.9): 2.3, 3.7	82 (7.7): 6.2, 9.5	29 (3.5): 2.4, 5.1
SAEs	120 (4.8): 4.0, 5.7	70 (2.9): 2.2, 3.6	80 (7.5): 6.0, 9.3	31 (3.8): 2.6, 5.3
AEs with fatal outcome	7 (0.3): 0.1, 0.6	2 (0.1): 0.0, 0.3	4 (0.4): 0.1, 1.0	0
AEs leading to discontinuation	17 (0.7): 0.4, 1.1	2 (0.1): 0.0, 0.3	5 (0.5): 0.2, 1.1	1 (0.1): 0.0, 0.7
AEs leading to dose adjustment	10 (0.4): 0.2, 0.7	0	4 (0.4): 0.1, 1.0	1 (0.1): 0.0, 0.7
AEs leading to dose interruption	419 (16.6): 15.2, 18.1	27 (1.1): 0.7, 1.6	122 (11.5): 9.6, 13.5	29 (3.5): 2.4, 5.1

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

Hepatobiliary toxicity

Table 51. Incidence, severity, and clinical impact of Hepatobiliary toxicity AESI by preferred term in Study O12301C (Safety set)

Clinical impact of Hepatobiliary toxicity AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Hepatobiliary toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**667 (26.4)**	**273 (11.2)**
Alanine aminotransferase increased	492 (19.5)	136 (5.6)
Aspartate aminotransferase increased	426 (16.9)	139 (5.7)
Gamma-glutamyltransferase increased	119 (4.7)	67 (2.7)
Blood alkaline phosphatase increased	76 (3.0)	62 (2.5)
Blood bilirubin increased	66 (2.6)	28 (1.1)
Hepatic steatosis	22 (0.9)	13 (0.5)
Bilirubin conjugated increased	19 (0.8)	11 (0.5)
Hepatotoxicity	15 (0.6)	1 (< 0.1)
Hyperbilirubinaemia	12 (0.5)	3 (0.1)
Hypertransaminasaemia	12 (0.5)	5 (0.2)
Hepatic cytolysis	11 (0.4)	12 (0.5)
Drug-induced liver injury	9 (0.4)	0
Liver disorder	8 (0.3)	10 (0.4)
Transaminases increased	8 (0.3)	3 (0.1)
Hypoalbuminaemia	7 (0.3)	5 (0.2)
Hepatic cyst	4 (0.2)	7 (0.3)
Blood bilirubin unconjugated increased	3 (0.1)	0
Non-alcoholic steatohepatitis	3 (0.1)	1 (< 0.1)
Ascites	2 (0.1)	6 (0.2)
Cholestasis	2 (0.1)	2 (0.1)
Hepatic calcification	2 (0.1)	0
Hepatic enzyme increased	2 (0.1)	2 (0.1)
Hepatic function abnormal	2 (0.1)	1 (< 0.1)
Hepatitis toxic	2 (0.1)	0
Autoimmune hepatitis	1 (< 0.1)	0
Hepatic mass	1 (< 0.1)	0
Hepatic pain	1 (< 0.1)	4 (0.2)
Hepatobiliary disease	1 (< 0.1)	0
Hepatomegaly	1 (< 0.1)	0
Jaundice	1 (< 0.1)	0
Jaundice cholestatic	1 (< 0.1)	1 (< 0.1)
Liver injury	1 (< 0.1)	0
Haemangioma of liver	0	2 (0.1)
Hepatic encephalopathy	0	1 (< 0.1)
Liver function test increased	0	1 (< 0.1)

Hepatobiliary toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Liver scan abnormal	0	1 (< 0.1)
CTCAE grade ≥ 3 AEs	**217 (8.6)**	**42 (1.7)**
Alanine aminotransferase increased	192 (7.6)	17 (0.7)
Aspartate aminotransferase increased	118 (4.7)	13 (0.5)
Gamma-glutamyltransferase increased	26 (1.0)	22 (0.9)
Hepatotoxicity	7 (0.3)	0
Blood bilirubin increased	5 (0.2)	1 (< 0.1)
Drug-induced liver injury	5 (0.2)	0
Hepatic cytolysis	3 (0.1)	1 (< 0.1)
Blood alkaline phosphatase increased	2 (0.1)	2 (0.1)
Hepatic function abnormal	2 (0.1)	0
Ascites	1 (< 0.1)	1 (< 0.1)
Autoimmune hepatitis	1 (< 0.1)	0
Bilirubin conjugated increased	1 (< 0.1)	0
Hepatitis toxic	1 (< 0.1)	0
Hepatobiliary disease	1 (< 0.1)	0
Hypertransaminasaemia	1 (< 0.1)	0
Jaundice cholestatic	1 (< 0.1)	1 (< 0.1)
Liver injury	1 (< 0.1)	0
Hepatic cyst	0	1 (< 0.1)
Hepatic encephalopathy	0	1 (< 0.1)
SAEs	**26 (1.0)**	**5 (0.2)**
Alanine aminotransferase increased	9 (0.4)	0
Drug-induced liver injury	6 (0.2)	0
Aspartate aminotransferase increased	5 (0.2)	0
Hepatotoxicity	5 (0.2)	0
Ascites	1 (< 0.1)	1 (< 0.1)
Autoimmune hepatitis	1 (< 0.1)	0
Hepatic cytolysis	1 (< 0.1)	1 (< 0.1)
Hepatic function abnormal	1 (< 0.1)	0
Hepatobiliary disease	1 (< 0.1)	0
Jaundice cholestatic	1 (< 0.1)	1 (< 0.1)
Liver injury	1 (< 0.1)	0
Non-alcoholic steatohepatitis	1 (< 0.1)	0
Hepatic cyst	0	1 (< 0.1)
Hepatic encephalopathy	0	1 (< 0.1)
Liver function test increased	0	1 (< 0.1)
AEs leading to discontinuation	**225 (8.9)**	**3 (0.1)**
Alanine aminotransferase increased	180 (7.1)	2 (0.1)
Aspartate aminotransferase increased	71 (2.8)	0
Hepatotoxicity	7 (0.3)	0
Hypertransaminasaemia	4 (0.2)	0
Blood bilirubin increased	3 (0.1)	0
Drug-induced liver injury	3 (0.1)	0

Hepatobiliary toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Gamma-glutamyltransferase increased	3 (0.1)	0
Hepatic cytolysis	2 (0.1)	0
Bilirubin conjugated increased	1 (< 0.1)	0
Hepatic function abnormal	1 (< 0.1)	0
Hepatitis toxic	1 (< 0.1)	0
Hepatobiliary disease	1 (< 0.1)	0
Hyperbilirubinaemia	1 (< 0.1)	1 (< 0.1)
Non-alcoholic steatohepatitis	1 (< 0.1)	0
Transaminases increased	1 (< 0.1)	0
Hepatic enzyme increased	0	1 (< 0.1)
AEs leading to dose adjustment	**66 (2.6)**	**0**
Alanine aminotransferase increased	49 (1.9)	0
Aspartate aminotransferase increased	16 (0.6)	0
Gamma-glutamyltransferase increased	5 (0.2)	0
Blood bilirubin increased	3 (0.1)	0
Blood alkaline phosphatase increased	1 (< 0.1)	0
Hyperbilirubinaemia	1 (< 0.1)	0
Hypertransaminasaemia	1 (< 0.1)	0
AEs leading to dose interruption	**313 (12.4)**	**10 (0.4)**
Alanine aminotransferase increased	255 (10.1)	7 (0.3)
Aspartate aminotransferase increased	171 (6.8)	7 (0.3)
Gamma-glutamyltransferase increased	17 (0.7)	3 (0.1)
Blood bilirubin increased	15 (0.6)	0
Hepatotoxicity	7 (0.3)	0
Blood alkaline phosphatase increased	5 (0.2)	2 (0.1)
Drug-induced liver injury	5 (0.2)	0
Hepatic cytolysis	5 (0.2)	0
Hypertransaminasaemia	5 (0.2)	0
Hyperbilirubinaemia	3 (0.1)	0
Bilirubin conjugated increased	2 (0.1)	0
Hepatitis toxic	2 (0.1)	0
Autoimmune hepatitis	1 (< 0.1)	0
Hepatic function abnormal	1 (< 0.1)	0
Hepatobiliary disease	1 (< 0.1)	0
Non-alcoholic steatohepatitis	1 (< 0.1)	0

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Figure 15. Kaplan-Meier plot of ALT/AST, grade 2 or higher, as time-of-first occurrence by treatment group in Study O12301C (Safety set based on cut-off date 11-Jan-2023)

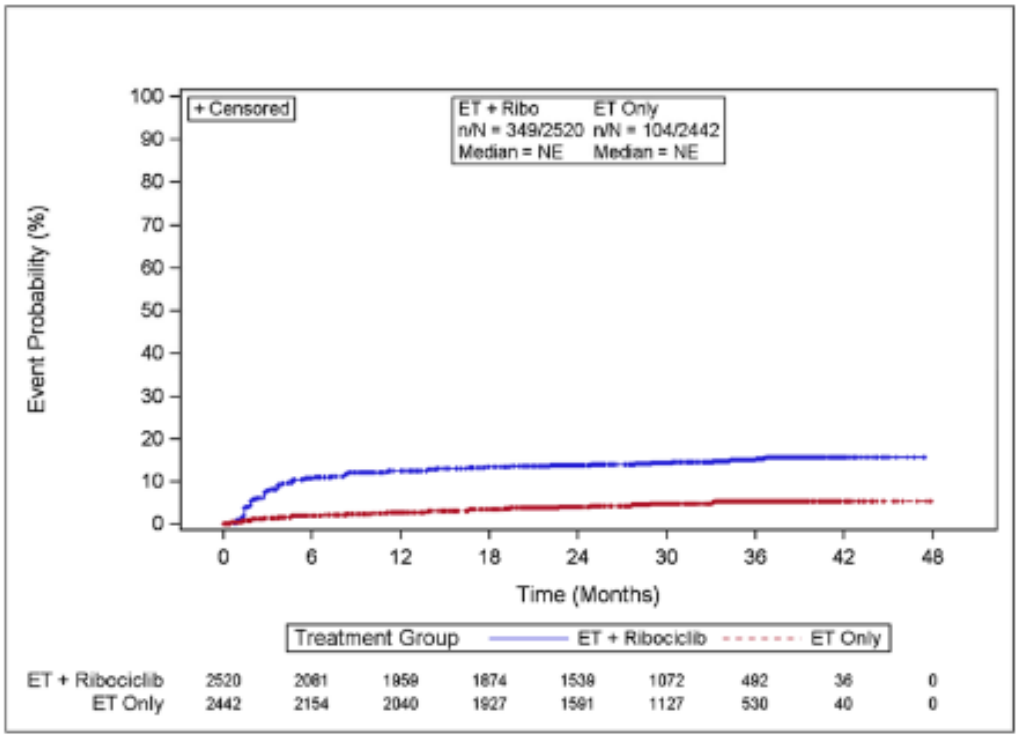


Table 52. Side-by side comparison of Hepatobiliary toxicity AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Hepatobiliary toxicity	Ribociclib plus ET N=2524 n (%): 95% CI	ET only N=2444 n (%): 95% CI	Ribociclib + ET N=1065 n (%): 95% CI	PBO + ET N=818 n (%): 95% CI
Total no. patients	**641 (25.4): 23.7, 27.1**	**260 (10.6): 9.4, 11.9**	**291 (27.3): 24.7, 30.1**	**160 (19.6): 16.9, 22.4**
Grade ≥ 3	209 (8.3): 7.2, 9.4	37 (1.5): 1.1, 2.1	141 (13.2): 11.3, 15.4	50 (6.1): 4.6, 8.0
SAEs	27 (1.1): 0.7, 1.6	4 (0.2): 0.0, 0.4	30 (2.8): 1.9, 4.0	7 (0.9): 0.3, 1.8
AEs with fatal outcome	0	0	3 (0.3): 0.1, 0.8	3 (0.4): 0.1, 1.1
AEs leading to discontinuation	225 (8.9): 7.8, 10.1	3 (0.1): 0.0, 0.4	69 (6.5): 5.1, 8.1	12 (1.5): 0.8, 2.5
AEs leading to dose adjustment	62 (2.5): 1.9, 3.1	0	36 (3.4): 2.4, 4.6	10 (1.2): 0.6, 2.2
AEs leading to dose interruption	303 (12.0): 10.8, 13.3	7 (0.3): 0.1, 0.6	121 (11.4): 9.5, 13.4	36 (4.4): 3.1, 6.0

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

Hepatobiliary toxicity AESI were reported more frequently in the ribociclib plus ET group (all grades, 26.4% and grade ≥ 3, 8.6%) relative to the ET only group (11.2% and 1.7%, respectively). Most of these events were increased ALT (all grades: 19.5% vs. 5.6%) and increased AST (16.9% vs. 5.7%).

The ALT/AST increased events were managed with protocol dose management guidance specific for hepatotoxicity. Few of these presented as SAE (increased ALT: 0.4% vs. 0; increased AST: 0.2% vs. 0).

Discontinuation of study treatment due to hepatobiliary toxicity events occurred in 8.9% of patients in the ribociclib plus ET group; predominantly due to increased ALT (7.1%) and increased AST (2.8%). In the ribociclib plus ET group, study treatment dose adjustments and dose interruptions were required for 66 patients (2.6%) and 313 patients (12.4%), respectively; again, primarily due to AEs of ALT increased and AST increased.

There were 9 patients (0.4%) in the ribociclib plus ET group who presented DILI. Of these 9, 6 patients (0.2%) were considered to have experienced serious DILI events and 5 patients (0.2%) had ≥ grade 3. Five patients had study treatment with ribociclib plus ET interrupted due to DILI, and 3 patients (0.1%) ultimately discontinued treatment due to DILI. As of DCO (21-Jul-2023), the reported DILI events were resolved in all patients, excluding 1 patient.

Renal toxicity

Table 53. Clinical impact of Renal toxicity AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Renal toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**152 (6.0)**	**58 (2.4)**
Blood creatinine increased	98 (3.9)	22 (0.9)
Glomerular filtration rate decreased	42 (1.7)	11 (0.5)
Blood urea increased	27 (1.1)	28 (1.1)
Acute kidney injury	7 (0.3)	3 (0.1)
Renal impairment	6 (0.2)	1 (< 0.1)
Renal failure	4 (0.2)	4 (0.2)
Creatinine renal clearance decreased	2 (0.1)	0
Azotaemia	1 (< 0.1)	0
Nephritis	1 (< 0.1)	0
Oliguria	1 (< 0.1)	0
Prerenal failure	1 (< 0.1)	0
Proteinuria	1 (< 0.1)	0
Tubulointerstitial nephritis	1 (< 0.1)	0
Blood creatinine abnormal	0	1 (< 0.1)
Hypercreatininaemia	0	2 (0.1)
CTCAE grade ≥ 3 AEs	**7 (0.3)**	**0**
Blood creatinine increased	3 (0.1)	0
Acute kidney injury	2 (0.1)	0
Glomerular filtration rate decreased	2 (0.1)	0
SAEs	**2 (0.1)**	**1 (< 0.1)**
Acute kidney injury	1 (< 0.1)	1 (< 0.1)
Blood creatinine increased	1 (< 0.1)	0
AEs leading to discontinuation	**9 (0.4)**	**0**
Blood creatinine increased	8 (0.3)	0
Glomerular filtration rate decreased	1 (< 0.1)	0

Renal toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
AEs leading to dose adjustment	**4 (0.2)**	**0**
Blood creatinine increased	2 (0.1)	0
Glomerular filtration rate decreased	1 (< 0.1)	0
Renal impairment	1 (< 0.1)	0
AEs leading to dose interruption	**22 (0.9)**	**0**
Blood creatinine increased	13 (0.5)	0
Glomerular filtration rate decreased	5 (0.2)	0
Renal impairment	2 (0.1)	0
Acute kidney injury	1 (< 0.1)	0
Prerenal failure	1 (< 0.1)	0
Renal failure	1 (< 0.1)	0

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Table 54. Side0by-side comparison of Renal toxicity AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Renal toxicity	Ribociclib plus ET N=2524 n (%): 95% CI	ET only N=2444 n (%): 95% CI	Ribociclib + ET N=1065 n (%): 95% CI	PBO + ET N=818 n (%): 95% CI
Total no. patients	**144 (5.7): 4.8, 6.7**	**49 (2.0): 1.5, 2.6**	**122 (11.5): 9.6, 13.5**	**34 (4.2): 2.9, 5.8**
Grade ≥ 3	7 (0.3): 0.1, 0.6	0	14 (1.3): 0.7, 2.2	7 (0.9): 0.3, 1.8
SAEs	3 (0.1): 0.0, 0.3	0	16 (1.5): 0.9, 2.4	5 (0.6): 0.2, 1.4
AEs with fatal outcome	0	0	0	0
AEs leading to discontinuation	7 (0.3): 0.1, 0.6	0	7 (0.7): 0.3, 1.3	1 (0.1): 0.0, 0.7
AEs leading to dose adjustment	3 (0.1): 0.0, 0.3	0	7 (0.7): 0.3, 1.3	2 (0.2): 0.0, 0.9
AEs leading to dose interruption	23 (0.9): 0.6, 1.4	0	24 (2.3): 1.4, 3.3	8 (1.0): 0.4, 1.9

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

QT interval prolongation

Table 55. Clinical impact of QT interval prolongation AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off)

QT interval prolongation Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**134 (5.3)**	**34 (1.4)**
Electrocardiogram QT prolonged	109 (4.3)	18 (0.7)
Syncope	17 (0.7)	14 (0.6)
Loss of consciousness	4 (0.2)	1 (< 0.1)
Cardiac arrest	1 (< 0.1)	0
Electrocardiogram repolarisation abnormality	1 (< 0.1)	1 (< 0.1)
Long QT syndrome	1 (< 0.1)	0
Ventricular tachycardia	1 (< 0.1)	0
CTCAE grade ≥ 3 AEs	**26 (1.0)**	**15 (0.6)**
Syncope	17 (0.7)	14 (0.6)
Electrocardiogram QT prolonged	7 (0.3)	1 (< 0.1)
Cardiac arrest	1 (< 0.1)	0
Loss of consciousness	1 (< 0.1)	0
SAEs	**5 (0.2)**	**2 (0.1)**
Syncope	4 (0.2)	2 (0.1)
Cardiac arrest	1 (< 0.1)	0
AEs leading to discontinuation	**10 (0.4)**	**0**
Electrocardiogram QT prolonged	7 (0.3)	0
Syncope	2 (0.1)	0
Ventricular tachycardia	1 (< 0.1)	0
AEs leading to dose adjustment	**3 (0.1)**	**0**
Electrocardiogram QT prolonged	3 (0.1)	0
AEs leading to dose interruption	**28 (1.1)**	**0**
Electrocardiogram QT prolonged	21 (0.8)	0
Syncope	7 (0.3)	0
AEs leading to death	**1 (< 0.1)**	**0**
Cardiac arrest	1 (< 0.1)	0

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Table 56. Notable ECG values (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Notable laboratory category	Ribociclib plus ET N=2525 n/m (%)	ET only N=2442 n/m (%)	Total N=4967 n/m (%)
QTcF			
New value > 450	240/2477 (9.7)	67/2365 (2.8)	307/4842 (6.3)
New value > 480	10/2493 (0.4)	4/2378 (0.2)	14/4871 (0.3)
New value > 500	3/2493 (0.1)	1/2378 (< 0.1)	4/4871 (0.1)
Increase from baseline of > 30	466/2493 (18.7)	167/2378 (7.0)	633/4871 (13.0)
Increase from baseline of > 60	19/2493 (0.8)	2/2378 (0.1)	21/4871 (0.4)

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

Table 57. Side-by-side comparison of QT interval prolongation AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
QT interval prolongation	Ribociclib plus ET N=2524 n (%): 95% CI	ET only N=2444 n (%): 95% CI	Ribociclib + ET N=1065 n (%): 95% CI	PBO + ET N=818 n (%): 95% CI
Total no. patients	**132 (5.2): 4.4, 6.2**	**30 (1.2): 0.8, 1.7**	**99 (9.3): 7.6, 11.2**	**29 (3.5): 2.4, 5.1**
Grade ≥ 3	25 (1.0): 0.6, 1.5	13 (0.5): 0.3, 0.9	34 (3.2): 2.2, 4.4	11 (1.3): 0.7, 2.4
SAEs	6 (0.2): 0.1, 0.5	1 (< 0.1): 0.0, 0.2	13 (1.2): 0.7, 2.1	3 (0.4): 0.1, 1.1
AEs with fatal outcome	1 (< 0.1): 0.0, 0.2	0	3 (0.3): 0.1, 0.8	0
AEs leading to discontinuation	11 (0.4) 0.2, 0.8	0	5 (0.5): 0.2, 1.1	3 (0.4): 0.1, 1.1
AEs leading to dose adjustment	3 (0.1): 0.0, 0.3	0	15 (1.4): 0.8, 2.3	2 (0.2): 0.0, 0.9
AEs leading to dose interruption	28 (1.1): 0.7, 1.6	0	20 (1.9): 1.2, 2.9	3 (0.4): 0.1, 1.1

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

2.5.3.5.3. Second primary malignancies

Table 58. Clinical impact of Second primary malignancies AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Second primary malignancies Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**48 (1.9)**	**49 (2.0)**
Meningioma	5 (0.2)	1 (< 0.1)
Papillary thyroid cancer	5 (0.2)	2 (0.1)
Malignant melanoma in situ	4 (0.2)	1 (< 0.1)
Malignant melanoma	3 (0.1)	0
Intraductal proliferative breast lesion	2 (0.1)	2 (0.1)
Acute myeloid leukaemia	1 (< 0.1)	3 (0.1)
Adenocarcinoma of colon	1 (< 0.1)	2 (0.1)
Basal cell carcinoma	1 (< 0.1)	7 (0.3)
Benign lymph node neoplasm	1 (< 0.1)	0
Bladder transitional cell carcinoma	1 (< 0.1)	3 (0.1)
Bowen's disease	1 (< 0.1)	1 (< 0.1)
Breast neoplasm	1 (< 0.1)	0
Clear cell renal cell carcinoma	1 (< 0.1)	0
Colon cancer stage 0	1 (< 0.1)	0
Colon cancer stage I	1 (< 0.1)	0
Colorectal cancer stage I	1 (< 0.1)	0
Colorectal carcinoma stage 0	1 (< 0.1)	0
Ductal adenocarcinoma of pancreas	1 (< 0.1)	0
Endometrial stromal sarcoma	1 (< 0.1)	0
Fallopian tube cancer	1 (< 0.1)	0
Glioblastoma	1 (< 0.1)	0
Glioma	1 (< 0.1)	0
Lip and/or oral cavity cancer recurrent	1 (< 0.1)	0
Malignant sweat gland neoplasm	1 (< 0.1)	0
Medullary thyroid cancer	1 (< 0.1)	0
Mucinous adenocarcinoma of appendix	1 (< 0.1)	0
Nasopharyngeal cancer	1 (< 0.1)	0
Neuroendocrine tumour	1 (< 0.1)	0
Ovarian epithelial cancer	1 (< 0.1)	0
Ovarian neoplasm	1 (< 0.1)	0
Pancreatic carcinoma	1 (< 0.1)	0
Rectal adenocarcinoma	1 (< 0.1)	1 (< 0.1)
Rectosigmoid cancer	1 (< 0.1)	0
Renal cancer	1 (< 0.1)	1 (< 0.1)

Second primary malignancies Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Squamous cell carcinoma	1 (< 0.1)	0
Squamous cell carcinoma of skin	1 (< 0.1)	0
Squamous cell carcinoma of the cervix	1 (< 0.1)	0
Acute promyelocytic leukaemia	0	1 (< 0.1)
Adenocarcinoma gastric	0	1 (< 0.1)
Cervix carcinoma stage 0	0	1 (< 0.1)
Chromophobe renal cell carcinoma	0	1 (< 0.1)
Colon cancer	0	1 (< 0.1)
Colon cancer stage II	0	1 (< 0.1)
Cutaneous lymphoma	0	1 (< 0.1)
Endometrial cancer	0	1 (< 0.1)
Extramammary Paget's disease	0	1 (< 0.1)
Gastric cancer	0	1 (< 0.1)
Gastrointestinal stromal tumour	0	1 (< 0.1)
Invasive ductal breast carcinoma	0	1 (< 0.1)
Lung adenocarcinoma	0	1 (< 0.1)
Malignant melanoma stage I	0	1 (< 0.1)
Myelodysplastic syndrome	0	3 (0.1)
Oesophageal adenocarcinoma	0	1 (< 0.1)
Ovarian cancer	0	1 (< 0.1)
Ovarian clear cell carcinoma	0	1 (< 0.1)
Plasma cell myeloma	0	1 (< 0.1)
Rectal cancer	0	1 (< 0.1)
Renal cell carcinoma	0	1 (< 0.1)
Squamous cell carcinoma of lung	0	1 (< 0.1)
Superficial spreading melanoma stage unspecified	0	2 (0.1)
CTCAE grade ≥ 3 AEs	**30 (1.2)**	**30 (1.2)**
SAEs	**33 (1.3)**	**34 (1.4)**
AEs leading to discontinuation	**25 (1.0)**	**17 (0.7)**
AEs leading to dose interruption	**11 (0.4)**	**9 (0.4)**

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 28-Aug-2023.

2.5.3.5.4. ILD / pneumonitis

Table 59. Clinical impact of ILD / Pneumonitis AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

ILD / Pneumonitis Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**39 (1.5)**	**22 (0.9)**
Pneumonitis	16 (0.6)	9 (0.4)
Pulmonary fibrosis	7 (0.3)	7 (0.3)
Radiation pneumonitis	6 (0.2)	2 (0.1)
Lung opacity	3 (0.1)	0
Lung infiltration	2 (0.1)	0
Bronchiolitis	1 (< 0.1)	1 (< 0.1)
Cystic lung disease	1 (< 0.1)	2 (0.1)
Interstitial lung disease	1 (< 0.1)	0
Pulmonary radiation injury	1 (< 0.1)	1 (< 0.1)
Pulmonary sarcoidosis	1 (< 0.1)	0
Radiation fibrosis – lung	1 (< 0.1)	1 (< 0.1)
Sarcoidosis	0	1 (< 0.1)
CTCAE grade ≥ 3 AEs	**0**	**2 (0.1)**
Pneumonitis	0	1 (< 0.1)
Pulmonary radiation injury	0	1 (< 0.1)
Radiation fibrosis – lung	0	1 (< 0.1)
SAEs	**1 (< 0.1)**	**1 (< 0.1)**
Pneumonitis	1 (< 0.1)	0
Pulmonary radiation injury	0	1 (< 0.1)
Radiation fibrosis – lung	0	1 (< 0.1)
AEs leading to discontinuation	**6 (0.2)**	**0**
Pneumonitis	5 (0.2)	0
Radiation pneumonitis	1 (< 0.1)	0
AEs leading to dose interruption	**4 (0.2)**	**0**
Bronchiolitis	1 (< 0.1)	0
Pneumonitis	1 (< 0.1)	0
Pulmonary fibrosis	1 (< 0.1)	0
Radiation pneumonitis	1 (< 0.1)	0
ILD / Pneumonitis Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Table 60. Side-by-side comparison of ILD/pneumonitis AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
ILD / pneumonitis	Ribociclib plus ET N=2524 n (%): 95% CI	ET only N=2444 n (%): 95% CI	Ribociclib + ET N=1065 n (%): 95% CI	PBO + ET N=818 n (%): 95% CI
Total no. patients	**39 (1.5): 1.1, 2.1**	**19 (0.8): 0.5, 1.2**	**17 (1.6): 0.9, 2.5**	**5 (0.6): 0.2, 1.4**
Grade ≥ 3	0	2 (0.1): 0.0, 0.3	4 (0.4): 0.1, 1.0	0
SAEs	1 (< 0.1): 0.0, 0.2	1 (< 0.1): 0.0, 0.2	1 (0.1): 0.0, 0.5	0
AEs with fatal outcome	0	0	1 (0.1): 0.0, 0.5	0
AEs leading to discontinuation	6 (0.2): 0.1, 0.5	0	5 (0.5): 0.2, 1.1	0
AEs leading to dose adjustment	0	0	1 (0.1): 0.0, 0.5	0
AEs leading to dose interruption	3 (0.1): 0.0, 0.3	0	3 (0.3): 0.1, 0.8	1 (0.1): 0.0, 0.7

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

2.5.3.5.5. Reproductive toxicity

Table 61. Clinical impact of Reproductive toxicity AESI by preferred term, irrespective of causality (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

Reproductive toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
All AEs	**32 (1.3)**	**27 (1.1)**
Mastitis	27 (1.1)	19 (0.8)
Accessory spleen	1 (< 0.1)	0
Dermoid cyst	1 (< 0.1)	0
Omphalitis	1 (< 0.1)	1 (< 0.1)
Polycystic liver disease	1 (< 0.1)	0
Retracted nipple	1 (< 0.1)	1 (< 0.1)
Sacralisation	1 (< 0.1)	0
BRCA1 gene mutation	0	1 (< 0.1)
BRCA2 gene mutation	0	1 (< 0.1)
Failure to thrive	0	1 (< 0.1)
Fibrous dysplasia of bone	0	1 (< 0.1)
Human chorionic gonadotropin increased	0	1 (< 0.1)
Neurofibromatosis	0	1 (< 0.1)
Nipple infection	0	1 (< 0.1)
Renal arteriovenous malformation	0	1 (< 0.1)
CTCAE grade ≥ 3 AEs	**8 (0.3)**	**7 (0.3)**
Mastitis	7 (0.3)	5 (0.2)
Polycystic liver disease	1 (< 0.1)	0
Failure to thrive	0	1 (< 0.1)
Renal arteriovenous malformation	0	1 (< 0.1)
SAEs	**5 (0.2)**	**5 (0.2)**
Mastitis	4 (0.2)	2 (0.1)
Polycystic liver disease	1 (< 0.1)	0

Reproductive toxicity Preferred term	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
BRCA1 gene mutation	0	1 (< 0.1)
BRCA2 gene mutation	0	1 (< 0.1)
Failure to thrive	0	1 (< 0.1)
Renal arteriovenous malformation	0	1 (< 0.1)
AEs leading to discontinuation	**2 (0.1)**	**1 (< 0.1)**
Mastitis	2 (0.1)	0
BRCA1 gene mutation	0	< 0.1)
BRCA2 gene mutation	0	1 (< 0.1)
AEs leading to dose interruption	**12 (0.5)**	**1 (< 0.1)**
Mastitis	12 (0.5)	1 (< 0.1)

Patients with multiple events in a grouping are counted only once in the grouping.
Patients with events in more than 1 category within a grouping are counted once in each of those categories.
AESI grouping terms are presented by preferred terms as sorted within the AESI grouping in descending frequency, as reported in the ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.
AESI groupings per eCRS released by Novartis dated 26-Aug-2023.

Table 62. Side-by-side comparison of Reproductive toxicity AESI by AE categories of Study O12301C vs. Pooled aBC Dataset (Safety set based on cut-off date 11-Jan-2023)

	Study O12301C		Pooled aBC Dataset	
Reproductive toxicity	Ribociclib plus ET N=2524 n (%): 95% CI	ET only N=2444 n (%): 95% CI	Ribociclib + ET N=1065 n (%): 95% CI	PBO + ET N=818 n (%): 95% CI
Total no. patients	**32 (1.3): 0.9, 1.8**	**25 (1.0): 0.7, 1.5**	**6 (0.6): 0.2, 1.2**	**6 (0.7): 0.3, 1.6**
Grade ≥ 3	8 (0.3): 0.1, 0.6	5 (0.2): 0.1, 0.5	1 (0.1): 0.0, 0.5	0
SAEs	5 (0.2): 0.1, 0.5	4 (0.2): 0.0, 0.4	0	0
AEs with fatal outcome	0	0	0	0
AEs leading to discontinuation	2 (0.1): 0.0, 0.3	1 (< 0.1): 0.0, 0.2	0	0
AEs leading to dose adjustment	0	0	0	0
AEs leading to dose interruption	12 (0.5): 0.2, 0.8	1 (< 0.1): 0.0, 0.2	1 (0.1): 0.0, 0.5	0

For Study O12301C MedDRA Version 25.1 is used for reporting and eCRS dated 16-Dec-2022. For the Pooled aBC Dataset, MedDRA Version 24.0 is used for reporting and eCRS dated 16-Jun-2021.

2.5.4. Serious adverse event/deaths/other significant events

2.5.4.1. Serious adverse events

Table 63. Serious adverse events by preferred term, irrespective of causality (≥ 3 patients / either group) (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

	Ribociclib plus ET N=2525				ET only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
No. patients with at least 1 TEAE	**357 (14.1)**	**252 (10.0)**	**44 (1.7)**	**11 (0.4)**	**256 (10.5)**	**192 (7.9)**	**26 (1.1)**	**4 (0.2)**
COVID-19	20 (0.8)	13 (0.5)	0	3 (0.1)	13 (0.5)	9 (0.4)	0	1 (< 0.1)
Pulmonary embolism	15 (0.6)	11 (0.4)	1 (< 0.1)	2 (0.1)	5 (0.2)	5 (0.2)	0	0
Pneumonia	14 (0.6)	12 (0.5)	0	0	9 (0.4)	7 (0.3)	0	0
Dyspnoea	12 (0.5)	9 (0.4)	0	0	5 (0.2)	3 (0.1)	0	0
COVID-19 pneumonia	9 (0.4)	5 (0.2)	0	3 (0.1)	5 (0.2)	4 (0.2)	1 (< 0.1)	0
Breast cellulitis	9 (0.4)	9 (0.4)	0	0	3 (0.1)	3 (0.1)	0	0
Alanine aminotransferase increased	9 (0.4)	1 (< 0.1)	7 (0.3)	0	0	0	0	0
Humerus fracture	8 (0.3)	7 (0.3)	0	0	4 (0.2)	3 (0.1)	0	0
Atrial fibrillation	7 (0.3)	5 (0.2)	1 (< 0.1)	0	8 (0.3)	7 (0.3)	0	0
Cellulitis	7 (0.3)	7 (0.3)	0	0	6 (0.2)	6 (0.2)	0	0
Cholelithiasis	7 (0.3)	6 (0.2)	1 (< 0.1)	0	5 (0.2)	5 (0.2)	0	0
Pyrexia	7 (0.3)	2 (0.1)	0	0	1 (< 0.1)	1 (< 0.1)	0	0
Urinary tract infection	6 (0.2)	6 (0.2)	0	0	3 (0.1)	3 (0.1)	0	0
Drug-induced liver injury	6 (0.2)	2 (0.1)	3 (0.1)	0	0	0	0	0
Papillary thyroid cancer	5 (0.2)	5 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Postoperative wound infection	5 (0.2)	5 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
Aspartate aminotransferase increased	5 (0.2)	2 (0.1)	3 (0.1)	0	0	0	0	0
Hepatotoxicity	5 (0.2)	3 (0.1)	2 (0.1)	0	0	0	0	0
Cerebrovascular accident	5 (0.2)	2 (0.1)	0	0	1 (< 0.1)	0	1 (< 0.1)	0
Diarrhoea	5 (0.2)	3 (0.1)	0	0	0	0	0	0
Osteoarthritis	4 (0.2)	4 (0.2)	0	0	4 (0.2)	4 (0.2)	0	0
Appendicitis	4 (0.2)	3 (0.1)	1 (< 0.1)	0	2 (0.1)	2 (0.1)	0	0
Syncope	4 (0.2)	4 (0.2)	0	0	2 (0.1)	2 (0.1)	0	0
	Ribociclib plus ET N=2525				ET only N=2442			
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Acute myocardial infarction	4 (0.2)	1 (< 0.1)	3 (0.1)	0	0	0	0	0
Erysipelas	4 (0.2)	2 (0.1)	0	0	3 (0.1)	2 (0.1)	0	0
Mastitis	4 (0.2)	2 (0.1)	0	0	2 (0.1)	2 (0.1)	0	0
Pneumonia viral	4 (0.2)	0	0	0	3 (0.1)	1 (< 0.1)	0	0
Suspected COVID-19	4 (0.2)	0	0	0	1 (< 0.1)	0	0	0
Lymphoedema	3 (0.1)	3 (0.1)	0	0	2 (0.1)	2 (0.1)	0	0
Pyelonephritis	3 (0.1)	3 (0.1)	0	0	2 (0.1)	2 (0.1)	0	0
Radius fracture	3 (0.1)	3 (0.1)	0	0	2 (0.1)	2 (0.1)	0	0
Breast fibrosis	3 (0.1)	3 (0.1)	0	0	1 (< 0.1)	1 (< 0.1)	0	0
Cholecystitis acute	3 (0.1)	3 (0.1)	0	0	1 (< 0.1)	1 (< 0.1)	0	0
Urosepsis	3 (0.1)	2 (0.1)	1 (< 0.1)	0	1 (< 0.1)	1 (< 0.1)	0	0
Anaemia	3 (0.1)	1 (< 0.1)	0	0	2 (0.1)	1 (< 0.1)	1 (< 0.1)	0
Bacteraemia	3 (0.1)	1 (< 0.1)	2 (0.1)	0	0	0	0	0
Cholecystitis chronic	3 (0.1)	2 (0.1)	1 (< 0.1)	0	0	0	0	0
Constipation	3 (0.1)	3 (0.1)	0	0	0	0	0	0
Hypokalaemia	3 (0.1)	3 (0.1)	0	0	0	0	0	0
Spinal compression fracture	3 (0.1)	2 (0.1)	1 (< 0.1)	0	0	0	0	0
Spinal cord compression	3 (0.1)	1 (< 0.1)	2 (0.1)	0	0	0	0	0
Malignant melanoma	3 (0.1)	2 (0.1)	0	0	0	0	0	0
Myocardial ischaemia	3 (0.1)	1 (< 0.1)	0	0	1 (< 0.1)	1 (< 0.1)	0	0
Foot fracture	3 (0.1)	1 (< 0.1)	0	0	0	0	0	0
Device related infection	2 (0.1)	1 (< 0.1)	1 (< 0.1)	0	3 (0.1)	3 (0.1)	0	0
Post procedural infection	2 (0.1)	2 (0.1)	0	0	3 (0.1)	3 (0.1)	0	0
Respiratory failure	2 (0.1)	0	2 (0.1)	0	3 (0.1)	0	2 (0.1)	1 (< 0.1)
Hypertension	2 (0.1)	1 (< 0.1)	0	0	3 (0.1)	2 (0.1)	0	0
Cataract	2 (0.1)	0	0	0	3 (0.1)	2 (0.1)	0	0
Abdominal pain	1 (< 0.1)	1 (< 0.1)	0	0	3 (0.1)	3 (0.1)	0	0

Preferred term	Ribociclib plus ET N=2525				ET only N=2442			
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Acute myeloid leukaemia	1 (< 0.1)	0	1 (< 0.1)	0	3 (0.1)	1 (< 0.1)	2 (0.1)	0
Cardiac failure congestive	1 (< 0.1)	1 (< 0.1)	0	0	3 (0.1)	2 (0.1)	0	1 (< 0.1)
Myocardial infarction	1 (< 0.1)	1 (< 0.1)	0	0	3 (0.1)	2 (0.1)	0	1 (< 0.1)
Sepsis	1 (< 0.1)	0	1 (< 0.1)	0	3 (0.1)	0	2 (0.1)	1 (< 0.1)
Small intestinal obstruction	1 (< 0.1)	1 (< 0.1)	0	0	3 (0.1)	3 (0.1)	0	0
Depression	0	0	0	0	3 (0.1)	1 (< 0.1)	2 (0.1)	0
Fall	0	0	0	0	3 (0.1)	3 (0.1)	0	0
Myelodysplastic syndrome	0	0	0	0	3 (0.1)	0	3 (0.1)	0

Preferred terms are sorted in descending frequency based on frequency in ribociclib plus ET group.
MedDRA Version 26.0 has been used for reporting.

2.5.4.2. Deaths

Table 64. All deaths by primary reason for death and preferred term (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set

All death Reason for death	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)	Total N=4967 n (%)
Total no. of patients who died overall	**83 (3.3)**	**89 (3.6)**	**172 (3.5)**
Primary reason of death			
Disease recurrence/progression	**58 (2.3)**	**73 (3.0)**	**131 (2.6)**
Adverse event	**16 (0.6)**	**4 (0.2)**	**20 (0.4)**
COVID-19	3 (0.1)	1 (< 0.1)	4 (0.1)
COVID-19 pneumonia	3 (0.1)	0	3 (0.1)
Pulmonary embolism	2 (0.1)	0	2 (< 0.1)
Acute myocardial infarction	1 (< 0.1)	0	1 (< 0.1)
Brain oedema	1 (< 0.1)	0	1 (< 0.1)
Cardiac arrest	1 (< 0.1)	0	1 (< 0.1)
Cardio-respiratory arrest	1 (< 0.1)	0	1 (< 0.1)
Cardiogenic shock	1 (< 0.1)	0	1 (< 0.1)
Cardiovascular insufficiency	1 (< 0.1)	0	1 (< 0.1)
Pneumonia	1 (< 0.1)	0	1 (< 0.1)
Road traffic accident	1 (< 0.1)	0	1 (< 0.1)
Cardiac failure congestive	0	1 (< 0.1)	1 (< 0.1)
Myocardial infarction	0	1 (< 0.1)	1 (< 0.1)
Sepsis	0	1 (< 0.1)	1 (< 0.1)
All death Reason for death	**Ribociclib plus ET N=2525 n (%)**	**ET only N=2442 n (%)**	**Total N=4967 n (%)**
Other	**9 (0.4)**	**12 (0.5)**	**21 (0.4)**
Acute myeloid leukaemia	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Death	1 (< 0.1)	6 (0.2)	7 (0.1)
General physical health deterioration	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Lower respiratory tract infection	1 (< 0.1)	0	1 (< 0.1)
Lung neoplasm malignant	1 (< 0.1)	0	1 (< 0.1)
Malignant melanoma	1 (< 0.1)	0	1 (< 0.1)
Pancreatic carcinoma	1 (< 0.1)	0	1 (< 0.1)
Pulmonary embolism	1 (< 0.1)	0	1 (< 0.1)
Rectosigmoid cancer	1 (< 0.1)	0	1 (< 0.1)
Adenocarcinoma gastric	0	1 (< 0.1)	1 (< 0.1)
Cardiac arrest	0	1 (< 0.1)	1 (< 0.1)
Fungal sepsis	0	1 (< 0.1)	1 (< 0.1)
Sepsis	0	1 (< 0.1)	1 (< 0.1)

Other as per-protocol are defined as SAEs collected after 36 months + 30 days and not related to study treatment.

As of the data cut-off date of 21-Jul- 2023, a total of 83 (3.3%) and 89 (3.6%) patients died during the study in the ribociclib + ET and ET only groups, respectively. The main cause of death during the study in

both the ribociclib + ET and ET only treatment groups, was disease recurrence/progression (2.3 % vs. 3.0%). Deaths due to AEs in the ribociclib + ET arm was 0.6%.

Nine patients (0.4%) in the ribociclib + ET group and 12 patients (0.5%) in the ET only group died due to reasons 'other' than disease recurrence/progression or AE. The reasons for the 'other' deaths reported in the ribociclib + ET arm were (one patient each): acute myeloid leukaemia, lung neoplasm malignant, malignant melanoma and rectosigmoid cancer, and pulmonary embolism.

Table 65. On-treatment deaths (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set

On-treatment death Reason for death	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)	Total N=4967 n (%)
Total no. patients who died on treatment	**20 (0.8)**	**9 (0.4)**	**29 (0.6)**
Primary reason of death			
Disease recurrence/progression	**9 (0.4)**	**4 (0.2)**	**13 (0.3)**
Adverse event	**11 (0.4)**	**4 (0.2)**	**15 (0.3)**
COVID-19	3 (0.1)	1 (< 0.1)	4 (0.1)
COVID-19 pneumonia	3 (0.1)	0	3 (0.1)
Pulmonary embolism	2 (0.1)	0	2 (< 0.1)
Brain oedema	1 (< 0.1)	0	1 (< 0.1)
Cardiac arrest	1 (< 0.1)	0	1 (< 0.1)
Road traffic accident	1 (< 0.1)	0	1 (< 0.1)
Cardiac failure congestive	0	1 (< 0.1)	1 (< 0.1)
Myocardial infarction	0	1 (< 0.1)	1 (< 0.1)
Sepsis	0	1 (< 0.1)	1 (< 0.1)
Other	**0**	**1 (< 0.1)**	**1 (< 0.1)**
Death	0	1 (< 0.1)	1 (< 0.1)

[1]On-treatment deaths are defined as occurring on or after treatment start date and up to 30 days after 36 months of treatment or earlier treatment discontinuation.

A total of 20 patients (0.8%) in the ribociclib + ET group and nine patients (0.4%) in the ET only group died within 36 months of treatment plus 30 days of safety follow-up.

In the ribociclib + ET group 10 (0.4%) on-treatment deaths occurred during the ribociclib treatment period. The remaining seven (0.3%) occurred > 30 days from the discontinuation of ribociclib, whilst continuing to receive treatment with ET.

On-treatment death due to AE was reported for 11 patients (0.4%) in the ribociclib + ET group and for four patients (0.2%) in the ET only group.

On-treatment death due to disease recurrence/progression occurred in 9 patients (0.4%) in the ribociclib + ET group vs. 4 patients (0.2%) in the ET only group.

2.5.5. Laboratory findings

2.5.5.1. Haematology

The most common worst-post-baseline grade 1 / 2 haematological abnormalities in the ribociclib plus ET group (≥ 10.0% difference relative to ET only group) were: decreased leukocytes (+23.3%), decreased hemoglobin (+21.3%), decreased platelets (+15.1%), and decreased neutrophils (+15.0%).

Grade 3 haematological abnormalities in the ribociclib plus ET group (≥ 10.0% difference relative to ET only group) were: decreased neutrophils (+41.5%), decreased leukocytes (+26.8%), and decrease lymphocytes (+12.4%). The highest number of patients (in both treatment groups) with grade-4 hematological abnormalities were decreased lymphocytes (2.7% of ribociclib plus ET patients and 2.3% of ET only patients).

Table 66 Worst post-baseline hematology value (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set)

	Ribociclib plus ET N=2525			ET only N=2442		
Notable laboratory category	Grade 1 / 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 1 / 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Activated partial thromboplastin time (sec) Hyper Grade	11 (0.4)	0	0	8 (0.3)	0	0
Hemoglobin (g/L) Hyper Grade	91 (3.6)	3 (0.1)	0	162 (6.6)	4 (0.2)	0
Hemoglobin (g/dL) Hypo Grade	1178 (46.7)	14 (0.6)	0	619 (25.4)	8 (0.3)	0
Leukocytes (10E9/L) Hyper Grade	0	4 (0.2)	0	0	1 (< 0.1)	0
Leukocytes (10E9/L) Hypo Grade	1714 (67.9)	688 (27.3)	5 (0.2)	1089 (44.6)	12 (0.5)	2 (0.1)
Lymphocytes (10E9/L) Hyper Grade	24 (1.0)	10 (0.4)	0	49 (2.0)	6 (0.3)	0
Lymphocytes (10E9/L) Hypo Grade	1980 (78.4)	413 (16.4)	67 (2.7)	1998 (81.8)	98 (4.0)	55 (2.3)
Neutrophils (10E9/L) Hypo Grade	1225 (48.5)	1083 (42.9)	55 (2.2)	818 (33.5)	35 (1.4)	6 (0.3)
Platelets (10E9/L) Hypo Grade	705 (27.9)	9 (0.4)	1 (< 0.1)	312 (12.8)	7 (0.3)	1 (< 0.1)
Prothrombin intl. normalized ratio (sec) Hyper Grade	5 (0.2)	1 (< 0.1)	0	3 (0.1)	2 (0.1)	0

Baseline is defined as the last non-missing value prior to the start date of study treatment.
Percentages are based on N.
Patients are counted only for the worst grade observed post-baseline.
Laboratory assessments performed after on-treatment period are not summarized.
CTCAE Version 4.03 is used for reporting.

2.5.5.2. Clinical chemistry

Grade 1 / 2 increased creatinine (+20.9%) were the only clinical chemistry parameter reported in a higher proportion of patients (difference ≥ 10%) who received ribociclib plus ET, compared with patients who received ET only. The frequency of remaining post-baseline biochemical abnormalities was similar by group. There were no grade 3 clinical chemistry abnormalities in ribociclib plus ET group with a≥ 10% difference relative to ET only group.

The most common grade 4 clinical chemistry abnormalities (with incidences ≥ 1.0%) reported in ribociclib plus ET group were increased ALT (1.5% vs. < 0.1%) and increased urate (1.5% vs. 1.8%).

2.5.5.3. Intrinsic factors

2.5.5.3.1. AESI by sex and menopausal status

Table 67. AESI by sex and menopausal status in Study O12301C (safety set based on cut-off date 11-Jan-2023)

	Premenopausal Women		Postmenopausal Women		Men	
AESI grouping – n (%)	Ribociclib plus ET N=1106	ET only N=1072	Ribociclib plus ET N=1408	ET only N=1363	Ribociclib plus ET N=10	ET only N=9
Myelosuppression - Neutropenia	733 (66.3)	66 (6.2)	832 (59.1)	44 (3.2)	4 (40.0)	1 (11.1)
Myelosuppression - Leukopenia	248 (22.4)	67 (6.3)	334 (23.7)	44 (3.2)	2 (20.0)	0
Myelosuppression - Anaemia	79 (7.1)	32 (3.0)	131 (9.3)	41 (3.0)	0	1 (11.1)
Myelosuppression - Thrombocytopenia	57 (5.2)	25 (2.3)	104 (7.4)	27 (2.0)	1 (10.0)	1 (11.1)
Infections	543 (49.1)	388 (36.2)	659 (46.8)	449 (32.9)	2 (20.0)	2 (22.2)
Hepatobiliary toxicity	253 (22.9)	113 (10.5)	387 (27.5)	145 (10.6)	2 (20.0)	2 (22.2)
Renal toxicity	31 (2.8)	9 (0.8)	111 (7.9)	40 (2.9)	2 (20.0)	0
QT interval prolongation	62 (5.6)	18 (1.7)	69 (4.9)	12 (0.9)	1 (10.0)	0
Second primary alignancies	18 (1.6)	16 (1.5)	28 (2.0)	29 (2.1)	0	0
ILD / pneumonitis	15 (1.4)	5 (0.5)	24 (1.7)	14 (1.0)	0	0
Reproductive toxicity	17 (1.5)	12 (1.1)	15 (1.1)	13 (1.0)	0	0

2.5.5.3.2. AESI by age

Table 68. AESI by sex and menopausal status in Study O12301C (Safety set based on cut-off date 11-Jan-2023)

	< 65 Years		≥ 65 Years	
AESI grouping – n (%)	Ribociclib plus ET N=2122	ET only N=2093	Ribociclib plus ET N=402	ET only N=351
Myelosuppression - Neutropenia	1338 (63.1)	102 (4.9)	231 (57.5)	9 (2.6)
Myelosuppression - Leukopenia	481 (22.7)	97 (4.6)	103 (25.6)	14 (4.0)
Myelosuppression - Anaemia	148 (7.0)	55 (2.6)	62 (15.4)	19 (5.4)
Myelosuppression - Thrombocytopenia	120 (5.7)	46 (2.2)	42 (10.4)	7 (2.0)
Infections	1024 (48.3)	729 (34.8)	180 (44.8)	110 (31.3)
Hepatobiliary toxicity	528 (24.9)	216 (10.3)	114 (28.4)	44 (12.5)
Renal toxicity	96 (4.5)	30 (1.4)	48 (11.9)	19 (5.4)
QT interval prolongation	107 (5.0)	26 (1.2)	25 (6.2)	4 (1.1)
Second primary malignancies	39 (1.8)	31 (1.5)	7 (1.7)	14 (4.0)
ILD / pneumonitis	32 (1.5)	16 (0.8)	7 (1.7)	3 (0.9)
Reproductive toxicity	30 (1.4)	23 (1.1)	2 (0.5)	2 (0.6)

Anaemia, thrombocytopenia and renal toxicity were more frequently reported in patients ≥65 years compared to patients <65 years.

2.5.5.3.3. Adverse events by age range (CLEE011O12301C safety set)

Table 69. Adverse events by age range (CLEE011O12301C Safety set based on cut-off date 11-Jan-2023)

	ET + Ribociclib				ET alone			
MedDRA Terms	**Age <65 N=2123**	**Age 65-74 N=346**	**Age 75-84 N=53**	**Age 85+ N=3**	**Age <65 N=2091**	**Age 65-74 N=288**	**Age 75-84 N=63**	**Age 85+ N=0**
	n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Total AEs	2081 (98.0)	338 (97.7)	52 (98.1)	3 (100)	1843 (88.1)	252 (87.5)	50 (79.4)	0
Serious AEs – Total	277 (13.0)	66 (19.1)	13 (24.5)	1 (33.3)	204 (9.8)	39 (13.5)	13 (20.6)	0
- Fatal	7 (0.3)	4 (1.2)	0	0	3 (0.1)	1 (0.3)	0	0
- Hospitalization/prolong existing hospitalization	247 (11.6)	60 (17.3)	12 (22.6)	1 (33.3)	189 (9.0)	37 (12.8)	13 (20.6)	0
- Life-threatening	14 (0.7)	5 (1.4)	0	0	11 (0.5)	1 (0.3)	1 (1.6)	0
- Disability/incapacity	5 (0.2)	2 (0.6)	0	0	2 (0.1)	2 (0.7)	0	0
- Other (medically significant)	47 (2.2)	9 (2.6)	2 (3.8)	0	23 (1.1)	5 (1.7)	2 (3.2)	0
AE leading to discontinuation (Ribociclib and/or ET)	409 (19.3)	92 (26.6)	21 (39.6)	2 (66.7)	111 (5.3)	20 (6.9)	3 (4.8)	0
Psychiatric disorders	534 (25.15)	69 (19.94)	13 (24.53)	0	514 (24.58)	45 (15.63)	12 (19.05)	0
Nervous system disorders	856 (40.32)	135 (39.02)	21 (39.62)	1 (33.33)	685 (32.76)	84 (29.17)	19 (30.16)	0
Accidents and injuries	203 (9.56)	43 (12.43)	8 (15.09)	0	161 (7.70)	30 (10.42)	8 (12.70)	0
Cardiac disorders	149 (7.02)	41 (11.85)	7 (13.21)	0	132 (6.31)	18 (6.25)	6 (9.52)	0

	ET + Ribociclib				ET alone			
MedDRA Terms	**Age <65 N=2123**	**Age 65-74 N=346**	**Age 75-84 N=53**	**Age 85+ N=3**	**Age <65 N=2091**	**Age 65-74 N=288**	**Age 75-84 N=63**	**Age 85+ N=0**
	n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Vascular disorders	707 (33.30)	101 (29.19)	23 (43.40)	1 (33.33)	725 (34.67)	75 (26.04)	18 (28.57)	0
Cerebrovascular disorders	26 (1.22)	13 (3.76)	3 (5.66)	0	27 (1.29)	10 (3.47)	2 (3.17)	0
Infections and infestations	1064 (50.12)	160 (46.24)	24 (45.28)	1 (33.33)	762 (36.44)	94 (32.64)	20 (31.75)	0
Anticholinergic syndrome	567 (26.71)	90 (26.01)	12 (22.64)	1 (33.33)	354 (16.93)	37 (12.85)	8 (12.70)	0
Quality of life decreased*	NA	NA	NA	NA	NA	NA	NA	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	220 (10.36)	45 (13.01)	7 (13.21)	0	138 (6.60)	21 (7.29)	4 (6.35)	0

* There were no associated Adverse Events reported for 'quality of life' in CLEE011O12301C study

2.5.5.3.4. By disease stages

Table 70. AESI by AJCC Anatomic Stage Group in Study O12301C (Safety set based on cut-off date 11-Jan-2023)

	AJCC Anatomic Stage Group II		AJCC Anatomic Stage Group III	
AESI grouping – n (%)	Ribociclib plus ET N=996	ET only N=1007	Ribociclib plus ET N=1518	ET only N=1431
Myelosuppression - Neutropenia	591 (59.3)	41 (4.1)	971 (64.0)	70 (4.9)
Myelosuppression - Leukopenia	202 (20.3)	38 (3.8)	380 (25.0)	73 (5.1)
Myelosuppression - Anaemia	76 (7.6)	36 (3.6)	132 (8.7)	38 (2.7)
Myelosuppression - Thrombocytopenia	62 (6.2)	24 (2.4)	99 (6.5)	29 (2.0)
Infections	461 (46.3)	357 (35.5)	738 (48.6)	481 (33.6)
Hepatobiliary toxicity	271 (27.2)	105 (10.4)	368 (24.2)	155 (10.8)
Renal toxicity	64 (6.4)	20 (2.0)	80 (5.3)	29 (2.0)
QT interval prolongation	49 (4.9)	11 (1.1)	83 (5.5)	19 (1.3)
Second primary malignancies	17 (1.7)	17 (1.7)	28 (1.8)	28 (2.0)
ILD / pneumonitis	12 (1.2)	6 (0.6)	27 (1.8)	13 (0.9)
Reproductive toxicity	14 (1.4)	8 (0.8)	18 (1.2)	17 (1.2)

2.5.6. Safety in special populations

2.5.6.1. Renal impairment

Table 71. Renal impairment, as normal, mild, moderate vs. severe (based on cut-off date 11-Jan-2023)

	Normal renal function		Mild renal impairment		Moderate renal impairment	
AESI grouping – n (%)	Ribociclib plus ET N=1434	ET only N=1385	Ribociclib plus ET N=1009	ET only N=973	Ribociclib plus ET N=72	ET only N=81
Myelosuppression – Neutropenia	925 (64.5)	70 (5.1)	608 (60.3)	37 (3.8)	31 (43.1)	4 (4.9)
Myelosuppression - Leukopenia	326 (22.7)	70 (5.1)	236 (23.4)	35 (3.6)	20 (27.8)	6 (7.4)
Myelosuppression - Anaemia	114 (7.9)	31 (2.2)	81 (8.0)	35 (3.6)	13 (18.1)	8 (9.9)
Myelosuppression-Thrombocytopenia	86 (6.0)	29 (2.1)	67 (6.6)	20 (2.1)	7 (9.7)	4 (4.9)
Infections	680 (47.4)	486 (35.1)	482 (47.8)	329 (33.8)	40 (55.6)	23 (28.4)
Hepatobiliary toxicity	379 (26.4)	144 (10.4)	240 (23.8)	107 (11.0)	21 (29.2)	9 (11.1)
Renal toxicity	29 (2.0)	17 (1.2)	93 (9.2)	23 (2.4)	22 (30.6)	9 (11.1)
QT interval prolongation	79 (5.5)	12 (0.9)	50 (5.0)	18 (1.8)	3 (4.2)	0
Second primary malignancies	21 (1.5)	28 (2.0)	25 (2.5)	15 (1.5)	0	2 (2.5)
ILD / pneumonitis	18 (1.3)	10 (0.7)	20 (2.0)	8 (0.8)	1 (1.4)	1 (1.2)
Reproductive toxicity	18 (1.3)	13 (0.9)	13 (1.3)	12 (1.2)	1 (1.4)	0

2.5.6.2. Hepatic impairment

Table 72. AESI by baseline hepatic impairment in Study O12301C (Safety set (based on cut-off date 11-Jan-2023)

	Normal hepatic function		Mild hepatic impairment		Moderate hepatic impairment	
AESI grouping – n (%)	Ribociclib plus ET N=2290	ET only N=2202	Ribociclib plus ET N=221	ET only N=229	Ribociclib plus ET N=3	ET only N=9
Myelosuppression - Neutropenia	1422 (62.1)	99 (4.5)	140 (63.3)	11 (4.8)	2 (66.7)	0
Myelosuppression - Leukopenia	514 (22.4)	101 (4.6)	66 (29.9)	10 (4.4)	1 (33.3)	0
Myelosuppression - Anaemia	197 (8.6)	69 (3.1)	11 (5.0)	5 (2.2)	0	0
Myelosuppression - Thrombocytopenia	146 (6.4)	48 (2.2)	15 (6.8)	5 (2.2)	0	0
Infections	1094 (47.8)	760 (34.5)	101 (45.7)	73 (31.9)	2 (66.7)	5 (55.6)
Hepatobiliary toxicity	548 (23.9)	205 (9.3)	91 (41.2)	55 (24.0)	1 (33.3)	0
Renal toxicity	134 (5.9)	44 (2.0)	9 (4.1)	5 (2.2)	0	0
QT interval prolongation	120 (5.2)	28 (1.3)	12 (5.4)	2 (0.9)	0	0
Second primary malignancies	38 (1.7)	41 (1.9)	7 (3.2)	4 (1.7)	0	0
ILD / pneumonitis	34 (1.5)	18 (0.8)	5 (2.3)	1 (0.4)	0	0
Reproductive toxicity	29 (1.3)	21 (1.0)	3 (1.4)	3 (1.3)	0	1 (11.1)

2.5.7. Discontinuation due to adverse events

Table 73. Adverse events leading to discontinuation irrespective of causality, by preferred term and maximum grade (in greater than or equal to 3 patients in either group) (safety set based on cut-off date 11-Jan-2023)

	Ribociclib + ET N=2524				ET only N=2444			
Preferred Term	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Number of patients with at least one TEAE	523 (20.7)	202 (8.0)	35 (1.4)	6 (0.2)	129 (5.3)	35 (1.4)	5 (0.2)	3 (0.1)
Alanine aminotransferase increased	176 (7.0)	77 (3.1)	19 (0.8)	0	2 (0.1)	1 (0.0)	0	0
Aspartate aminotransferase increased	71 (2.8)	29 (1.1)	7 (0.3)	0	0	0	0	0
Arthralgia	34 (1.3)	4 (0.2)	0	0	46 (1.9)	9 (0.4)	0	0
Fatigue	24 (1.0)	5 (0.2)	0	0	2 (0.1)	0	0	0
Neutropenia	16 (0.6)	13 (0.5)	2 (0.1)	0	0	0	0	0
Neutrophil count decreased	14 (0.6)	12 (0.5)	0	0	0	0	0	0
Nausea	13 (0.5)	1 (0.0)	0	0	2 (0.1)	0	0	0
Hepatotoxicity	8 (0.3)	4 (0.2)	2 (0.1)	0	0	0	0	0
Asthenia	8 (0.3)	4 (0.2)	0	0	1 (0.0)	0	0	0
Rash	8 (0.3)	2 (0.1)	0	0	2 (0.1)	0	0	0
Headache	7 (0.3)	2 (0.1)	0	0	5 (0.2)	0	0	0
Blood magnesium decreased	7 (0.3)	0	0	0	0	0	0	0
COVID-19	6 (0.2)	2 (0.1)	1 (0.0)	2 (0.1)	1 (0.0)	0	1 (0.0)	0
Diarrhoea	6 (0.2)	2 (0.1)	0	0	2 (0.1)	0	0	0
Electrocardiogram QT prolonged	6 (0.2)	1 (0.0)	0	0	0	0	0	0
Blood creatinine increased	6 (0.2)	0	0	0	0	0	0	0
Hypomagnesaemia	6 (0.2)	0	0	0	0	0	0	0
Pulmonary embolism	5 (0.2)	3 (0.1)	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	0	0
Alopecia	5 (0.2)	0	0	0	0	0	0	0
Pneumonitis	5 (0.2)	0	0	0	0	0	0	0

Preferred Term	Ribociclib + ET N=2524 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	ET only N=2444 All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Papillary thyroid cancer	4 (0.2)	4 (0.2)	0	0	0	0	0	0
Gamma-glutamyltransferase increased	4 (0.2)	3 (0.1)	0	0	0	0	0	0
Anxiety	4 (0.2)	1 (0.0)	0	0	1 (0.0)	0	0	0
Hyperkalaemia	4 (0.2)	1 (0.0)	0	0	0	0	0	0
Hypertransaminasaemia	4 (0.2)	1 (0.0)	0	0	0	0	0	0
Acute myocardial infarction	3 (0.1)	1 (0.0)	2 (0.1)	0	0	0	0	0
COVID-19 pneumonia	3 (0.1)	1 (0.0)	1 (0.0)	1 (0.0)	0	0	0	0
Syncope	3 (0.1)	3 (0.1)	0	0	0	0	0	0
Depression	3 (0.1)	2 (0.1)	0	0	0	0	0	0
Drug-induced liver injury	3 (0.1)	2 (0.1)	0	0	0	0	0	0
Malignant melanoma	3 (0.1)	2 (0.1)	0	0	0	0	0	0
White blood cell count decreased	3 (0.1)	2 (0.1)	0	0	0	0	0	0
Blood bilirubin increased	3 (0.1)	1 (0.0)	0	0	0	0	0	0
Dyspnoea	3 (0.1)	0	0	0	2 (0.1)	1 (0.0)	0	0
Hypercalcaemia	3 (0.1)	0	0	0	0	0	0	0
Pyrexia	3 (0.1)	0	0	0	0	0	0	0
Myalgia	2 (0.1)	1 (0.0)	0	0	6 (0.2)	2 (0.1)	0	0
Acute myeloid leukaemia	1 (0.0)	0	1 (0.0)	0	3 (0.1)	1 (0.0)	2 (0.1)	0
Osteoporosis	0	0	0	0	3 (0.1)	0	0	0

Preferred terms are sorted in descending frequency based on frequency in ribociclib + ET arm.
MedDRA Version 25.1 has been used for reporting.

AEs leading to study treatment discontinuation were reported more commonly in the ribociclib + ET group (20.7%) compared to the ET only group (5.3%). The most commonly reported AEs leading to study treatment drug discontinuation in the ribociclib + plus ET group were ALT increased (7.0%), AST increased (2.8%), arthralgia (1.3%), fatigue (1.0%), neutropenia (0.6%), neutrophil count decreased (0.6%), and nausea (0.5%).

2.5.7.1. Dose modification

Table 74. Study treatment modifications (final iDFS analysis, 21-Jul-2023 data cut-off) (Safety set

Modification Reason for modification	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Ribociclib		
No. patients who have dose reduction	675 (26.7)	–
Adverse event	576 (22.8)	–
Dosing error	89 (3.5)	–
Technical problem	4 (0.2)	–
Physician decision	15 (0.6)	–
Other	7 (0.3)	–
No. patients who have dose interruption	2173 (86.1)	–
Adverse event	1671 (66.2)	–

Modification Reason for modification	Ribociclib plus ET N=2525 n (%)	ET only N=2442 n (%)
Dosing error	1189 (47.1)	–
Dispensing error	96 (3.8)	–
Technical problem	90 (3.6)	–
Physician decision	306 (12.1)	–
Logistical issue	724 (28.7)	–
Other	531 (21.0)	–
NSAI		
No. patients who have dose interruption	1123 (44.5)	872 (35.7)
Adverse event	281 (11.1)	134 (5.5)
Dosing error	881 (34.9)	705 (28.9)
Dispensing error	57 (2.3)	40 (1.6)
Technical problem	15 (0.6)	16 (0.7)
Physician decision	70 (2.8)	40 (1.6)
Logistical issue	61 (2.4)	55 (2.3)
Other	137 (5.4)	110 (4.5)
Missing	2 (0.1)	0
No. patients who switched NSAI treatment	99 (3.9)	122 (5.0)

For patients who did not tolerate the protocol-specified dosing schedule, a single dose reduction of ribociclib from 400 mg to 200 mg is permitted to allow the patient to continue study treatment.
Multiple entries for interruption on consecutive days with different reasons will be counted as separate interruptions.

2.5.8. Post marketing experience

The cumulative exposure is estimated to approximately 127,528 PTY (Kisqali PSUR 2023).

Cumulatively, since the time of the first marketing authorisation approval of Kisqali (in 2017), two new safety signals were identified (interstitial lung disease [ILD]/pneumonitis and toxic epidermal necrolysis [TEN]).

2.5.9. Discussion on clinical safety

The safety data base is considered of an acceptable magnitude for detecting any changes to the already known safety characterisation of ribociclib and/or identifying new safety concerns including those potentially related to this new patient population.

The median duration of exposure to ribociclib in the NATALEE study was 33 months, with 69.4% patients exposed for >24 months and 42.8% patients exposed for >36 months.

Overall, the presented data on patient exposure evoked no concern and the methodology for selection of ADRs was considered acceptable.

Observations on the overall safety data are in line with the known safety profile of ribociclib. A clear difference relative the comparator in terms of frequency of AE reports is noted in regard to e.g. SAEs (14.1% and 10.5%, respectively), severity (Grade 3 and 4), AEs leading to discontinuations and dose interruptions.

Neutropenia was the most frequently reported adverse reaction (62.5%) and a grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 45.1% of patients receiving Kisqali plus aromatase inhibitor (AI). As expected with the lower starting dose of ribociclib 400 mg QD, less overall incidences and incidences of grade ≥ 3 Neutropenia AESI were observed compared to that in the pooled aBC dataset treated with 600 mg QD. Events of neutropenia leading to treatment discontinuation are considered acceptable for the ribociclib + ET arm. It has previously been concluded when ribociclib was initially approved in patients with aBC, that the risk of neutropenia is not regarded as any major concern since it is considered to be manageable with the risk minimisation measures laid out in the SmPC. This

conclusion is applicable also for the eBC population. No new concern is evoked based on the submitted data. The risk of neutropenia is substantially addressed in sections 4.2, 4.4 and 4.8 of the Kisqali SmPC. Myelosuppression is included in the safety specification of the RMP as an important identified risk.

Events in the Anaemia AESI were 8.6% in the ribociclib + ET group vs. 3.2% in the ET only group. The vast majority of events by PT were anaemia (8.4% vs. 3.0%, respectively). Events of Grade≥ 3 were similar between the two arms (0.3% in both arms). In three patients in each arm, anaemia events were considered SAEs (0.3%). There were two patients (0.1%) who discontinued study treatment in the ribociclib + ET group due to anaemia.

Events in the Thrombocytopenia AESI were 6.4% in the ribociclib + ET group vs. 2.3% in the ET only group. By PT, these were limited to thrombocytopenia (4.4% vs. 1.8%) and decreased platelet count (2.1% vs. 0.5%). Events of Grade ≥ 3) were reported with a similar proportion (0.2% and 0.1%, respectively). There were no SAEs reported. In one patient who had a Grade ≥3 event of thrombocytopenia, a vitreous haemorrhage occurred which were not assessed as related by the investigator. One patient (< 0.1%) discontinued study treatment in the ribociclib + ET group due to thrombocytopenia.

Events of Infections AESI were 49.6% in the ribociclib + ET group vs. 36.2% in the ET only group. The majority were reported for COVID-19 infection (21.3% vs. 14.1%, respectively). Following in frequency, the next most frequent reported infection was UTI (6.5% vs. 5.1%). The remaining PTs presented infrequently, and no obvious pattern can be identified. Infections are a known ADR to ribociclib and included in the ADR table (with frequency `Very common´). The following infections are detailed: urinary tract infections, respiratory tract infections, gastroenteritis and sepsis.

Hepatobiliary toxicity AESI were reported more frequently in the ribociclib plus ET group (all grades, 26.4% and grade ≥ 3, 8.6%) as compared to the ET only group (11.2% and 1.7%, respectively). The majority of event were increased ALT (all grades: 19.5% vs. 5.6%) and increased AST (16.9% vs. 5.7%).

Few of these presented as SAE (increased ALT: 0.4% vs. 0; increased AST: 0.2% vs. 0).

Discontinuation of study treatment due to hepatobiliary toxicity events occurred in 8.9% of patients in the ribociclib plus ET group; predominantly due to increased ALT (7.1%) and increased AST (2.8%). In the ribociclib plus ET group, study treatment dose adjustments and dose interruptions were required for 66 patients (2.6%) and 313 patients (12.4%), respectively; again, primarily due to AEs of ALT increased and AST increased.

There were 9 patients (0.4%) in the ribociclib plus ET group who presented DILI. Of these 9, 6 patients (0.2%) were considered to have experienced serious DILI events and 5 patients (0.2%) had ≥ grade 3. Five patients had study treatment with ribociclib plus ET interrupted due to DILI, and 3 patients (0.1%) ultimately discontinued treatment due to DILI. As of the data cut-off (21-Jul-2023), the reported DILI events were resolved in all but one patient.

Hepatobiliary toxicity is addressed in sections 4.2, 4.4 and 4.8 of the Kisqali SmPC and it is considered that the risk minimisation measures currently included in the SmPC pertaining to the aBC population (dose modifications, monitoring of liver function tests and management of events of hepatobiliary toxicities) are considered also sufficiently applicable to the eBC population.

Events in the Renal toxicity AESI were 6.0% in the ribociclib + ET group vs. 2.4% in the ET only group, consisting mainly of reports by PT of `increased blood creatinine´ (3.9% vs. 0.9%). Decreased glomerular filtration rate was more frequent in the ribociclib plus ET group (1.7% vs. 0.5%). In the ribociclib + ET arm, one patient (<0.1%) had an SAE of AKI and one patient (< 0.1%) had an SAE of increased blood creatinine. Out of seven (0.3%) Renal toxicity AESI grade ≥ 3 in ribociclib + ET arm, three events were increased blood creatinine, two were decreased glomerular filtration rate, and twowere

AKI. AEs of renal toxicity leading to treatment discontinuation was acceptable (0.4% in the ribociclib + ET arm).

Based on the submitted data no new concern has been evoked. Renal toxicity is adequately addressed in sections 4.2 (renal impairment, 4.4 (Blood creatinine increase and Renal impairment) and included in Table 7 in section 4.8 (SOC Investigations: Blood creatinine increase). In addition, Renal toxicity is an important potential risk already included in the safety specifications.

Overall, in the NATALEE study QT interval prolongation AESI were more commonly reported in the ribociclib + ET group compared with the ET only group (5.3% vs. 1.4%). The most frequently reported in both the ribociclib + ET and ET only treatment groups were ECG QT prolonged (4.3% and 0.7% respectively). The incidences of ≥ grade 3 QT interval prolongation AESI were 1.0% in the ribociclib + ET and 0.6% ET only group. The most common ≥ grade 3 QT prolongation event reported in both the ribociclib + ET group (in 0.7% of patients) and ET only group (in 0.6% of patients) was syncope. Study treatment was discontinued for 10 patients (0.4%) in the ribociclib + ET group due to ECG QT prolonged; for 4 patients (0.2%) due to syncope; and for 1 patient (< 0.1%) each due to cardiac arrest. A total of four patients (0.2%) had an SAE of syncope, and one patient (<0.1%) had an SAE of cardiac arrest. There were no cardiac sudden deaths or TdP reported. The known risk of QT interval prolongation is extensively addressed in sections 4.2, 4.4, 4.8 and 5.1 of the Kisqali SmPC, and already included in the safety specifications as an important identified risk. ECG should be assessed before initiating treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle, then as clinically indicated (see sections 4.2, 4.4 and 4.8 of the SmPC). In patients with early breast cancer, appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali. Based on the observed QT prolongation during treatment, treatment with Kisqali may have to be interrupted, reduced or discontinued (see sections 4.2, 4.4, 4.8 and 5.2 of the SmPC).

The overall proportion of patients with ILD / pneumonitis AESI was 1.5% vs. 0.9% in the ribociclib + ET arm vs. the ET only arm. The majority were events of pneumonitis (0.6% vs. 0.4%, respectively). There were no events of Grade ≥3 and one SAE reported in the ribociclib + ET arm. The proportion of events of ILD/pneumonitis leading to treatment discontinuation is acceptable (0.2%). ILD/pneumonitis is adequately addressed in section 4.2 and 4.4 of the Kisqali SmPC and the table in section 4.8 has now been updated with `ILD/pneumonitis´ also for the eBC population. Two new safety signals were identified (interstitial lung disease [ILD]/pneumonitis and toxic epidermal necrolysis [TEN]) that eventually were added as postmarketing ADRs in the Kisqali prescribing information with communication within the Warning and precaution section 4.4. Further to the post marketing setting assessment, section 4.4 and 4.8 have been updated with ILD/Pneumonitis and TEN for the aBC population (with a frequency of `Common´ and `Not known´, respectively).

Events in the Reproductive toxicity AESI were reported in 1.3% in the R + ET arm and 1.1% in the ET only arm, including Grade ≥3 (0.3% in both arms) and SAEs (0.2% in both arms). The proportion of AEs leading to discontinuation was low (0.1%). The observed increase in reports of reproductive toxicity in the eBC population compared to the pooled aBC population (1.3% vs. 0.6%) including Grade ≥3 (0.3% vs. 0.1%) and SAEs (0.2% vs. 0%), is however noted. Upon further review, the incidence of the events appears to be driven primarily by the PT 'mastitis' with the incidence of all grades 27 (1.1%) vs 3 (0.3%) in eBC and aBC patients, respectively. In the NATALEE study `Mastitis´ was reported in 27 patients (1.1%) in the ribociclib + ET arm compared to 17 patients (0.7%) in the control arm (see Table 61.). The observed incidence of mastitis in the eBC population could be explained by factors such as patients with eBC start ribociclib treatment in adjuvant setting, meaning they have recently had neoadjuvant

chemotherapy, surgery and radiation. Moreover, it does not appear that mastitis occurred in the context of myelosuppression (i.e. neutropenia). It is concluded that a causal association between ribociclib and `mastitis´ cannot be established at this point. Reproductive toxicity is addressed in sections 4.4, 4.6 and 5.3. In addition, Reproductive toxicity is an important identified risk already included in the safety specification and will be monitored.

Overall, no new concerns have been identified in relation to the AESIs.

Dose reduction due to adverse events, regardless of causality, occurred in 22.8% of patients receiving Kisqali plus AI in the phase III clinical study. Permanent discontinuation was reported in 19.7% of patients receiving Kisqali plus AI in the phase III clinical study.

2.5.10. Conclusions on clinical safety

The safety profile as characterised in the pivotal study is mainly in line with what has previously been established for ribociclib in combination with ET in aBC patients, despite differences in safety profiles due to differences in the study designs, patient populations and disease setting, background therapies, comorbidities, risk factors, starting dose and duration of exposure. Moreover, no new safety concerns have been identified. The safety profile is acceptable for the proposed use.

2.5.11. 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 MAH submitted an updated RMP version 8.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Safety concerns

No changes were proposed by the MAH to the summary of safety concerns. The summary of safety concerns is as follows:

Table 75: 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

Pharmacovigilance plan

There are no additional pharmacovigilance activities.

Risk minimisation measures

Table 76 ***Summary of pharmacovigilance activities and risk minimization activities by safety concerns***

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Myelosuppression	Section 4.2, Section 4.4 and Section 4.8 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hepatobiliary toxicity	Section 4.2, Section 4.4, Section 4.8, and Section 5.3 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
QT interval prolongation	Section 4.2, Section 4.4, Section 4.5, Section 4.8, Section 5.1 and Section 5.3 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Reproductive Toxicity	Section 4.4, Section 4.6 and Section 5.3 of the SmPC and Section 2 of PL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Renal toxicity	Section 4.2, Section 4.8 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in Japanese patients	Currently available data are limited and do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated as well as the Annex IID. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the

representative(s) of the Netherlands.

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:
A consultation with the target patient population regarding the readability of the Package Leaflet (PL) for Kisqali was conducted as part of the original Marketing Authorisation Application. The new information proposed in the PL included in this type II variation maintain the currently approved layout and format and are not considered to require further consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final approved indication is:

Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see SmPC section 5.1 for selection criteria).

3.1.2. Available therapies and unmet medical need

According to current ESMO and NCCN 2024 clinical guidelines (Loibl S, Ann Oncol. 2024) pre- and postmenopausal women with HR-positive eBC are recommended adjuvant ET, consisting of tamoxifen or an AI + an LHRH for men and premenopausal women and either an AI or tamoxifen, alone or as sequential treatment, for postmenopausal women.

In 2022, Verzenios was approved for use in patients with early breast cancer at `high risk of recurrence´. High risk of recurrence is defined by clinical and pathological features: either $\geq$4 pALN (positive axillary lymph nodes), or 1-3 pALN and at least one of the following criteria: tumour size $\geq$5 cm or histological grade 3 (Verzenios-H-C-004302-II-0013).

Despite adjuvant therapies, which are normally considered for patients at risk for recurrence, approximately 30-60% of patients with stage II and III BC still relapse. The risk of recurrence in patients with HR-positive, HER-2 negative eBC is highest during the first 5 years after diagnosis, but >50% of those who recur will recur ≥ 5 years from diagnosis (Pan et al 2017). Therefore, there is a need to further improve outcomes in this patient population with new treatment options that can prevent recurrence and, eventually, death.

3.1.3. Main clinical studies

This new indication is supported by a randomised, open-label, multi-centre, phase III study CLEE11O12301C (O12301C) with adjuvant treatment with ribociclib + ET vs. ET only in adult women and men with Stage II (excluding low risk of recurrence) and stage III eBC. In total, 5,101 patients entered the study and were randomised 1:1 to ribociclib + ET (n=2,549) or ET only (n=2,552).

3.2. Favourable effects

Primary analysis results are derived from the third interim analysis (IA3) as of DCO 11 Jan 2023, with 426 PFS events and median duration from randomisation 34.0 months (range 21-48 months). At DCO, 515 (20.2%) patients in the ribociclib + ET arm had completed the full 36 months of ribociclib treatment.

HR for iDFS at the inferential IA3 was 0.748 (95% CI 0.618, 0.906, 1-sided p-value 0.0014) in favour of ribociclib + ET treatment. Median iDFS was not reached for any of the treatment arms. The 3-year iDFS rates were 90.4% (95% CI 88.6, 91.9) in the ribociclib + ET arm and 87.1% (95% CI 85.3, 88.8) in the ET only arm.

At the DCO of final iDFS analysis (DCO 21 Jul 2023), the HR for iDFS was 0.749 (95% CI 0.628, 0.892, 1-sided p-value 0.0006) in favour of ribociclib + ET treatment. The median time to iDFS was NR in both treatment arms. The 3-year iDFS rates were 90.7% (95% CI 89.3, 91.8) in the ribociclib + ET arm and 87.6% (95% CI 86.1, 88.9) in the ET only arm. HR for secondary endpoint RFS (not type 1 error controlled) at DCO for final iDFS analysis was 0.727 (95% CI 0.602, 0.887) in favour of the ribociclib + ET arm. The 3-year iDFS rate for RFS was 92.1% (95% CI 90.9, 93.2) in the ribociclib + ET arm and 89.1% (95% CI 87.6, 90.4) in the ET only arm, in line with the primary analysis.

HR for secondary endpoint DDFS (not type 1 error controlled) at DCO for final iDFS analysis was 0.749 (95% CI 0.623, 0.900), in favour of the ribociclib + ET treatment. The 3-year iDFS rate for DDFS was 91.5% (95% CI 90.2, 92.7) for the ribociclib + ET arm vs. 88.9% (95% CI 87.4, 90.2) for the ET only arm. This was in line with the primary analysis.

OS data were immature at DCO for the final iDFS analysis, with in total 172 (3.4%) events. HR for OS (not type 1 error controlled) was 0.892 (95% CI 0.661, 1.203)). Median OS was not reached for any of the treatment arms. The estimated 3-year OS rates were 97.0% (95% CI 96.2, 97.6) in the ribociclib + ET arm and 96.1% (95% CI 95.1, 96.9) in the ET only arm.

At the time of the most updated iDFS analysis, 78.3% of the patients had finished treatment with ribociclib. In total, 42.8% had completed the 3-year ribociclib treatment and 35.5% discontinued prematurely, mainly due to AEs (19.5%).

3.3. Uncertainties and limitations about favourable effects

At DCO for the final iDFS analysis only 42.8% of the patients had completed the full three years of ribociclib treatment and almost 80% of the patients had discontinued ribociclib with 35.5% of the patients discontinuing ribociclib early. The iDFS Kaplan-Meier curves continue to separate over time, indicating a sustained effect even after ribociclib discontinuation. While there are no signs of a detrimental effect on OS in ribociclib exposed patients, the OS data are still immature.

To further characterize the long-term benefit of ribociclib in this patient population more mature OS and iDFS data are considered relevant.

The following measures are considered necessary to address issues related to efficacy and safety:

Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of Kisqali in combination with an aromatase inhibitor for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence, the MAH should submit a 5-year follow-up of iDFS and OS in the NATALEE study.

3.4. Unfavourable effects

The safety evaluation is based on data from 2524 patients exposed to a starting dose of 400 mg ribociclib QD in combination with ET, and 2444 patients exposed to ET only.

The median duration of exposure to ribociclib across the study was 32.0 months, with 69.4% patients exposed for >24 months, and 42.8% patients completing the 36-month ribociclib regimen. Adverse events where a higher proportion of ribociclib plus ET-treated patients reported events, all grades, with a ≥ 10% relative difference to the ET only group, included:

Neutropenia: +38.5%; Decreased neutrophil count: +22.4%; Nausea: +15.5%; ALT increased: +13.9%; Leukopenia: +11.3%; AST increased: +11.2%; Alopecia: +10.6% and Arthralgia (43.3%). Hot flush (20.0%) were the only PTs reported in ≥ 20% of patients in the ET only group

The most common grade ≥ 3 AEs in the ribociclib + ET arm were neutropenia (28.0%), neutrophil count decreased (17.7%), ALT increased (7.6%), AST increased 4.7%), WBC decreased (3.7%), and leukopenia (3.7%).

Grade 3 AEs were reported in 57.9% of patients in the ribociclib + ET group (mainly neutropenia, neutrophil count decreased, and ALT increased) and 17.4% of patients in the ET only group.

Grade 4 AEs were reported in 5.3% of patients in the ribociclib + ET group and 1.6% of patients in the ET only group. Neutropenia (1.3%) and ALT increased (1.3%) were the most frequently reported grade 4 AE (with incidences ≥ 1.0%) in the ribociclib + ET group.

In 11 patients (0.4%) a grade 5 event (AE with fatal outcome) was reported in the ribociclib + ET group. Amongst causes were cardiac arrest, cardiogenic shock, concurrent brain oedema and epilepsy, pneumonia, pulmonary embolism, and road traffic accident.

SAEs were reported in 14.1% in the ribociclib + ET arm vs. 10.5% in the ET only group. The most commonly reported SAEs (in ≥10 patients) in the ribociclib + ET group were COVID-19 (0.8%), pneumonia (0.6%), pulmonary embolism (0.6%) and dyspnoea (0.5%).

A total of 83 (3.3%) and 89 (3.6%) patients died during the study in the ribociclib + ET and ET only groups, respectively. The main cause of death during the study in both the ribociclib + ET and ET only treatment groups, was disease recurrence/progression (2.3% vs. 3.0%). Deaths due to AEs in the ribociclib + ET arm was 0.6% with deaths related to COVID-19 accounting for about 0.1%.

AEs leading to study treatment discontinuation were reported more commonly in the ribociclib + ET group (20.8%) compared to the ET only group (5.5%).

Since this new patient population consists of patients presumed cured after their initial treatment for eBC, the risk of QT-prolongation and hepatobiliary toxicity warranted further consideration:

QT-prolongation

Overall, QT interval prolongation AESI were more commonly reported in the ribociclib + ET group compared with the ET only group (5.3% vs. 1.4%). The most frequently reported in both the ribociclib + ET and ET only treatment groups were ECG QT prolonged (4.3% and 0.7% respectively). The incidences of ≥ grade 3 QT interval prolongation AESI were 1.0% in the ribociclib + ET and 0.6% ET only group. The most common ≥ grade 3 QT prolongation event reported in both the ribociclib + ET group (in 0.7% of patients) and ET only group (in 0.6% of patients) was syncope.

Hepatobiliary toxicity

Events in the Hepatobiliary toxicity AESI were reported in 26.4% in the ribociclib + ET group vs. 11.2% in the ET only group and the majority by PT being increased ALT and AST. Events of Grade ≥3 were

reported in 8.6% and 1.7%, respectively. Hepatobiliary toxicity is addressed in sections 4.2, 4.4 and 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 77 Effects Table for study O12301C in early breast cancer (data cut-off: 11 Jan 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Full analysis set (FAS), n=5,101 participants						
			Ribociclib + ET N=2,549	ET only N=2,552		
iDFS (primary endpoint)	Invasive disease-free survival	HR (95% CI) p-value	0.748 (0.618-0.906) p=0.0014 (1-sided)		Final iDFS analysis HR (95% CI) 0.749 (0.628-0.892) p=0.0006 (1-sided)	Data at DCO for IA3 and Final iDFS analysis
OS (secondary endpoint)	Overall survival	Median, months	Not reached	Not reached	OS data immature (3.4%) Final data requested as PAES	Final iDFS analysis
		HR (95% CI)	0.892 (0.661-1.203)			
Unfavourable Effects n=2524 participants						
TEAEs	Neutropenia Arthralgia Nausea Fatigue ALT increased	%	41.0 36.5 23.0 21.9 18.9	2.9 42.5 7.5 12.7 5.2		
Grade 3 and 4	Any	%	56.9 and 5.2	16.1 and 1.6		
SAEs	Any	%	13.3	9.9		
TEAEs leading to discont.	Any ALT increased AST increased	%	20.7 7.0 2.8	5.3 0.1 0		
Deaths	Due to AEs	%	0.5	0.2		

Abbreviations: ET=endocrine therapy (letrozole, anastrozole); PD Disease recurrence/progression

Notes: All endpoints were investigator-assessed. Only iDFS was type 1 error controlled.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A statistically significant increase in iDFS with ribociclib + ET vs. ET only is shown in the intended population. The relative risk reduction with ribociclib + ET is 25.2%, whereas the absolute 3-years iDFS improvement is 3.3% (data at IA3). The final iDFS analysis confirmed these data. At the final iDFS analysis, almost 80% of the patients had discontinued ribociclib. Although only approximately half of them had completed the intended three years of ribociclib treatment and one fourth discontinued ribociclib prematurely due to AEs, the iDFS curves continued to separate over time. This indicates a sustained treatment effect even after ribociclib discontinuation. As expected in this early breast cancer setting, OS data are still immature but there are no signs of a detrimental effect on OS.

Given the approximately 3% absolute iDFS benefit at three years, a median of >30 months follow-up, a manageable toxicity with a relatively low proportion of on-treatment deaths (n=6 in the ribociclib + ET arm, n=4 in the ET only arm), and comparable proportions of patients who discontinued all treatment components (21.3% in the ribociclib + ET arm, 24.1% in the ET only arm, data at IA3), an effect of ribociclib as add-on to ET is considered established. The remaining uncertainty pertaining to a potential overall survival benefit is considered acceptable, however, to further characterize the long-term benefit of ribociclib in this patient population more mature OS and iDFS data are considered relevant.

These data will be provided as a post approval measure (PAES Annex IID condition) by June 2027.

Given the reduced dose recommended (400 mg QD) in this new patient population, an improved overall safety profile is recognised. The safety profile as characterised in the pivotal study is mainly in line with what has previously been established for ribociclib in combination with ET in aBC patients and no new safety concerns were identified. Given the established benefit, the safety profile is acceptable for the proposed use.

3.7.2. Balance of benefits and risks

Efficacy has been established with an acceptable safety profile. Therefore, the benefit/risk is considered positive for this new indication.

Third party intervention during the evaluation of Kisqali

On 19 October 2023, the CHMP received correspondence from a participant (hereafter referred to as "third party") in one of the MAH supported ribociclib studies. The third party expressed concerns about the efficacy and safety profile of Kisqali in the adjuvant treatment of breast cancer.

The CHMP considered the interventions and concluded that the concerns put forward by the third party were already addressed in the ongoing assessment and did not impact the CHMP conclusions.

3.7.3. Additional considerations on the benefit-risk balance

The current extension of indication application aims to treat early breast cancer in an adjuvant setting and would need to follow ICH M7 guidance for non-clinical development. The non-clinical development supporting the initial MA was conducted according to ICH S9 as ribociclib was intended for the treatment of advanced breast cancer. The N-nitrosoribociclib impurity (N-NRib) is present in trace amounts in ribociclib succinate drug substance and in Ribociclib 200 mg film-coated tablet. N-NRib was tested in three separate Ames tests, all concluding that N-NRib did not induce mutations under the test conditions.

However, N-NRib was determined to be mutagenic in an in vivo transgenic rodent (TGR) gene mutation assay (Muta™Mouse study). N-NRib limits need to be controlled using the carcinogenic potency categorization approach (CPCA) by applying a maximum acceptable intake (AI) of 400 ng/day (category 3). The applicant proposed changes to the quality module to include measures to minimize the formation of the N-NRib impurity and to ensure control of N-NRib in compliance with the acceptable intake of 400 ng/day throughout the product shelf-life and considering a Maximum Daily Dose (MDD) of 400 mg for the proposed early breast cancer indication.

A type II quality variation to amend the control strategy for the product, including more restrictive storage conditions and a shorter shelf-life has been submitted in Kisqali EMEA/H/C/004213/II/0054 procedure and adopted by CHMP on 17 October 2024. The proposed storage conditions have been proven to keep the levels of N-NRib below the established acceptable intake throughout the product shelf-life. The revised storage conditions are included in the SmPC and disseminated via a DHPC to inform the relevant stakeholders of the changes.

3.8. Conclusions

The Benefit Risk balance of Kisqali is positive.

The following measures are considered necessary to address issues related to efficacy:

In order to further evaluate the efficacy of Kisqali for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer, in combination with an aromatase inhibitor, the MAH should submit a 5-year follow-up of iDFS and OS in the NATALEE study. (Annex II.D)

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, II and IIIB

Extension of indication to include Kisqali in combination with an aromatase inhibitor for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence. In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

The indication is based on study CLEE011O12301C (NATALEE); This is a global, Phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with ET versus ET alone as adjuvant treatment in patients with HR-positive, HER2-negative, early breast cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated as well as Annex II.D. The Package Leaflet is updated in accordance. Version 8.2 of the RMP has also been submitted. In addition,

the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following new condition.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures.

The measure is a post-authorisation efficacy study (PAES) in accordance with the Commission Delegated Regulation (EU) No 357/2014.

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of Kisqali in combination with an aromatase inhibitor for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence, the MAH should submit a 5-year follow-up of iDFS and OS in the NATALEE study	June 2027