EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/156033/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Verzenios

International non-proprietary name: abemaciclib

Procedure No. EMEA/H/C/004302/II/0013

Note

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

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List of abbreviations

Term	Definition
ADR	adverse drug reaction
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
AI	aromatase inhibitors
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATAC	Arimidex, Tamoxifen, Alone or in Combination
$AUC_{T,ss}$	area under the concentration versus time curve during 1 dosing interval at steady state
A+ET	Abemaciclib in combination with endocrine therapy
BIG	Breast International Group
BMI	body mass index
C1-Ki67H	Cohort-1 Ki-67 high
CDK	cyclin-dependent kinase
CDK4 and CDK6	cyclin-dependent kinases 4 and 6
CHMP	Committee for Medical Products for Human Use
CI	confidence interval
$C_{max,ss,total}$	maximum concentration of total active species at steady state
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DFS	disease-free survival
DMC	Data Monitoring Committee
DRFS	distant relapse-free survival
DVT	deep vein thrombosis

EBC	early breast cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
enroll	The act of assigning a patient to a treatment. Patients who were enrolled in the trial are those who had been assigned to a treatment.
ER	oestrogen receptor
ESMO	European Society for Medical Oncology
ET	endocrine therapy
FACT-B	Functional Assessment of Cancer Therapy – Breast Cancer
FACT-ES	Functional Assessment of Cancer Therapy – Endocrine Subscale
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
GCP	good clinical practice: a set of government and corporate mandated guidelines that guides the conduct of clinical trials on a drug substance or medical device to ensure compliance with appropriate ethical and quality standards
G-CSF	granulocyte colony-stimulating factor
GI	Gastrointestinal
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2 negative
HR	hazard ratio
HR+	hormone receptor positive
ICH	International Conference on Harmonisation
IDFS	invasive disease-free survival
ILD	interstitial lung disease
investigator	a person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention-to-treat
Ki67H	Ki-67 high
MBC	metastatic breast cancer

MedDRA	**Med**ical **D**ictionary for **R**egulatory **A**ctivities: a standard coding terminology for adverse events used globally in compliance with International Conference for Harmonisation (ICH) guidelines.
NCCN	**National Comprehensive Cancer Network**
NDA	New Drug Application
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	overall survival
pALN	positive axillary lymph node
PE	pulmonary embolism
PFS	progression-free survival
PK	Pharmacokinetic
PopPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	preferred term
Rb	retinoblastoma protein
RMP	risk management plan
SAE	serious adverse event(s)
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SMQ	Standardized MedDRA Query
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
TE-SAE	Treatment-emergent serious adverse event
TNM	Tumour, node metastasis staging system
ULN	upper limit of normal
VTE	venous thromboembolic

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 10 November 2020 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 Verzenios in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence; as a consequence, section 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

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 P/0202/2019 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 24 September 2015 (EMEA/H/SA/2727/2/2015/III) and 23 February 2017 (EMEA/H/SAH/024/2/2016). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

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	10 November 2020
Start of procedure:	28 November 2020
CHMP Rapporteur Assessment Report	22 January 2021
PRAC Rapporteur Assessment Report	29 January 2021
PRAC members comments	3 February 2021
Updated PRAC Rapporteur Assessment Report	5 February 2021
PRAC Outcome	11 February 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 February 2021
Request for supplementary information (RSI)	25 February 2021
CHMP Rapporteur Assessment Report	26 May 2021
PRAC Rapporteur Assessment Report	27 May 2021
PRAC members comments	2 June 2021
Updated PRAC Rapporteur Assessment Report	3 June 2021
PRAC Outcome	10 June 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur Assessment Report	17 June 2021
Request for supplementary information (RSI)	24 June 2021
CHMP Rapporteur Assessment Report	22 September 2021
CHMP members comments	04 October 2021
Updated CHMP Rapporteur Assessment Report	08 October 2021
Request for supplementary information (RSI)	14 October 2021
CHMP Rapporteur Assessment Report	04 January 2022
CHMP members comments	17 January 2022
Updated CHMP Rapporteur Assessment Report	20 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	10 February 2022
PRAC Rapporteur Assessment Report	10 February 2022
CHMP members comments	14 February 2022
PRAC members comments	14 February 2022
Updated PRAC Rapporteur Assessment Report	18 February 2022
Updated CHMP Rapporteur Assessment Report	18 February 2022

Timetable	Actual dates
Opinion	24 February 2022
The CHMP adopted a report significant clinical benefit for Verzenios in comparison with existing therapies	24 February 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The currently applied indication for abemaciclib is:

Early Breast Cancer

Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see SmPC section 5.1).

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

Epidemiology and risk factors, screening tools/prevention

Breast cancer is the most frequently diagnosed cancer and leading cause of cancer death worldwide among women (Bray et al. 2018). About 1 in 8 women will develop invasive breast cancer over the course of their lifetimes (ACS 2019). In 2018, there were estimated to be 2.1 million new cases of breast cancer worldwide and 627,000 deaths (Bray et al. 2018). Over 90% of patients with breast cancer are diagnosed at an early stage (Cardoso et al. 2018b). The HR+, HER2- breast cancer subtype is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers and the most deaths from the disease (ACS 2019). Approximately 1% of all breast cancers diagnosed are in men (Senkus et al. 2015).

Biologic features

Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) breast cancer is frequently dependent on estrogen for survival and growth. Effects on proliferation involves stimulating progression through the G1 phase of the cell cycle, where the cyclin-dependent kinase (CDK)-4/6-retinoblastoma (pRB) axis is of central importance.

Mechanisms for interaction between the estrogen receptor (ER) and the cyclinD-CDK4/6-pRB axis include ER-dependent transcriptional induction of cyclin D1, but also cyclin D1 mimicking the normal action of estrogen by binding the ER receptor, thus forming a positive feedback loop. The relevance of cyclin D1 in HR+ breast cancer is supported by its frequent overexpression, often as a consequence of

genomic amplification of the CCND1 locus. The functionality of pRB and p16 expression (an inhibitor of the cyclin D-CDK4/6 interaction) are further factors of importance in this context.

Signalling through the PI3K/Akt/mTOR pathway also appears relevant in HR+ HER2- breast cancer. Activity can promote both proliferation by prevention of cyclin D1 degradation (via AKT), and growth through effects on metabolism and protein synthesis (via mTOR). The relevance of signalling in ER+ breast cancer is supported by frequent mutations in the PI3K catalytic subunit alpha. Also, amplification of FGFR1 is recurrent in HR+ HER2- breast cancer, with downstream signalling occurring via the PI3K/Akt/mTOR and mitogen-activated protein kinase (MAPK) pathways.

The mutational status of the ER receptor itself has emerged as a biological feature determining therapeutic efficacy in HR+ breast cancer. Although present at very low levels in endocrine-naïve tumours, mutations causing ligand-independent activation often develop during therapy with aromatase inhibitors. Methylation of the ER promoter and chromatin structure changes through epigenetic mechanisms can affect ER-dependent transcription.

Clinical presentation, diagnosis and stage/prognosis

Approximately 90% of patients with breast cancer are diagnosed at an early stage of their disease (Howlader et al. 2016). These patients are treated with curative intent and as such are candidates for local treatments including surgery followed very often by radiotherapy depending on the surgical approach and regional disease extension. After surgery, the indication of adjuvant systemic therapy is based on estimated individual risk of disease relapse and predicted sensitivity to available systemic therapies (i.e., ER/progesterone receptor and HER2 status). The most validated clinical and pathological features that may indicate a higher risk of distant disease relapse and therefore the need for adjuvant treatment include

- large primary tumor size
- involvement and degree of involvement of axillary lymph nodes, and
- high histologic grade.

Management

Patients with HR+, HER2- early breast cancer (EBC) are candidates for treatments with curative intent.

The decisions for which primary and subsequent treatments to administer are often based on multiple factors such as demography (for example, age) and clinicopathological risk factors indicative of risk of recurrence. Patients deemed to be at higher risk of recurrence will often receive more extensive and aggressive primary treatment in the form of chemotherapy (either neoadjuvant or adjuvant), surgery, and/or radiotherapy.

Clinical and pathological features that indicate a higher risk of distant disease relapse and the need for adjuvant treatment include large primary tumour size, involvement and degree of involvement of axillary lymph nodes, and high histologic grade. Based on the SOFT and TEXT clinical trial outcomes, young age, high grade tumour, and lymph node involvement are indicative of a high risk of recurrence in premenopausal patients.

Patients with lymph node-positive disease are most often candidates for chemotherapy. Standard adjuvant chemotherapy includes anthracycline and/or taxane-based regimen.

Adjuvant endocrine therapy (ET) is indicated in all patients with detectable endocrine receptor expression (defined as ≥1% of invasive cancer cells) irrespective of the use of chemotherapy. The choice of endocrine agent (tamoxifen and/or 1 of the 3 selective aromatase inhibitors: anastrozole,

letrozole, or exemestane) is primarily determined by the patient's menopausal status. Following primary treatment, patients with HR+ disease will receive ET for at least 5 years.

In premenopausal patients, standard ET includes tamoxifen with or without ovarian suppression for 5 to 10 years, or an aromatase inhibitor for 5 years with ovarian suppression in selected patients at high risk of disease recurrence based on the TEXT and SOFT studies. Ovarian suppression is achieved by ablation or treatment with an GnRH analogue.

In postmenopausal women, tamoxifen has mostly been replaced by the use of aromatase inhibitors as adjuvant treatment of EBC, however the use of aromatase inhibitors and tamoxifen either sequentially, as monotherapy, or extended therapy for a total duration of 5 to 10 years may also be a valid option. Bisphosphonates are also recommended for women with low oestrogen status, especially if the risk of relapse is deemed high, as bisphosphonates have been shown to improve OS.

Treatment of men with breast cancer is similar to that of postmenopausal women including consideration for androgen suppression using treatment with a GnRH analogue.

Based on Reinert and Barrios (2015), approximately 30% of all patients with HR+ EBC eventually experience disease relapse with metastases following treatment with curative intent with current standard of care adjuvant ET.

Following the introduction of tamoxifen in the 1970s for the adjuvant treatment of HR+ EBC, the standard of care in this setting was improved 2 decades later with introduction of the aromatase inhibitor (AI) drug class. At the time of the ATAC trial's first analysis, anastrozole showed better efficacy than tamoxifen in reducing the risk of disease recurrence or death, with a hazard ratio of 0.83 (95% CI: 0.71 to 0.96) and an absolute benefit of a 2% improvement in the 3-year DFS rate (89.4% versus 87.4%) in the adjuvant treatment of postmenopausal women with EBC. The result was even greater in the subgroup known to be HR+, in which the relative risk reduction in recurrence events for anastrozole against tamoxifen increased to 22% (Baum et al. 2002; Howell et al. 2005). Similar benefit was seen for letrozole over tamoxifen in the Breast International Group (BIG) 1-98 study (Thürlimann et al. 2005).

Since the introduction of the AIs in the early 2000s in HR+ EBC, little improvement in the outcomes for these patients has occurred. Risk assessment has been refined, and those patients with HR+, EBC at high risk of recurrence continue to have an unmet need. For example, patients with HR+ EBC with high (4 to 9 nodes) nodal involvement have 5-year distant recurrence risks as high as 22% (DRFS of 78%) (Pan et al. 2017).

Up to 20% of patients with HR+, HER2- disease may experience recurrence or have distant metastases with standard therapies alone in the first 10 years (EBCTCG 2015; Sparano et al. 2017). Based on unpublished analyses from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 and the West German Study (WSG) Plan B data, patients with clinical and pathological features similar to those enrolled in the current monarchE study were expected to have a 5-year Invasive Disease Free Survival rate of 80% to 85% (recurrence risk of at least 15% in 5 years) (Mamounas et al. 2005; Nitz et al. 2019). It is critical to improve upon the standard adjuvant therapy to prevent recurrence and metastatic disease for these patients.

2.1.2. About the product

Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of CDK4 and CDK6, which subsequently blocks proliferation by inhibiting progression from G1 phase into S and G2/M phases of the cell cycle.

Through phosphorylation of the growth suppressor retinoblastoma protein (Rb), CDK4, and CDK6 promote cell growth. In cancer cells, the CDK4/CDK6/Rb pathway is commonly altered. Abemaciclib inhibits CDK4 and CDK6 phosphorylation of Rb, thereby preventing cancer cell proliferation. Furthermore, abemaciclib blocks breast cancer cell progression and with longer treatment, can lead to prolonged antitumour effects by inducing senescence, apoptosis, and altering cellular metabolism.

Verzenios (abemaciclib) was first approved in the EU on Sept 27, 2018, for the indication:

treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

The MAH applied for extension of indication as follows:

Verzenios in combination with endocrine therapy (ET) is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section 5.1).

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

The CHMP adopted extension to the existing indication is:

Verzenios in combination with endocrine therapy (ET) is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section 5.1)**.**

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

Dosage

The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. The same dosage is proposed for the currently applied indication in early breast cancer. The duration of treatment for EBC should be two years, or until disease recurrence or unacceptable toxicity occurs.

For dosage of the concomitant endocrine therapy, section 4.2 of the SmPC for Verzenios refers to the SmPCs of the endocrine therapy combination partner.

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

The application is supported by the Phase 3 study I3Y-MC-JPCF (JPCF; monarchE), in which patients with HR+, HER2-, node positive early breast cancer at high risk of recurrence received abemaciclib in combination with endocrine therapy (standard of care; SOC) or placebo + endocrine therapy (SOC).

Two scientific advices in relation to the development of abemaciclib have been conducted by SAWP in September 2015 and February 2017. The latest advice in February 2017 concerned the indication assessed in this procedure.

With regard to patient population included based on ≥4 positive lymph nodes or 1-3 positive lymph nodes together with other risk factors, the resulting heterogeneity of the patient population was advised to be carefully considered. The endpoints and censoring rules are generally agreeable. The applicant was advised to include measures to minimize the bias due to the open-label design, e.g. radiographic assessment at fixed time points, etc. Concerns are related to the short follow-up times for planned interim analyses resulting in few patients with completed treatment and for the ones with completed treatment, very short follow-up after end of treatment. In addition, the applicant was advised to include the use of bisphosphonates as standard of care adjunct to endocrine treatment when not specifically contra-indicated.

2.1.4. General comments on compliance with GCP

The monarchE study was stated to be conducted in compliance with the principles of Good Clinical Practice (GCP).

2.2. Non-clinical aspects

2.2.1. Introduction

The prior submission package was adequate to support an advanced cancer patient population, such as metastatic breast cancer. For use in an indication that is less advanced, such as early breast cancer, ICH S9 indicates that sponsors should consider the extent of the already available clinical and nonclinical safety packages. Based on this guidance, the MAH has conducted an additional set of studies that provide data on:

- longer treatment duration in animals
- carcinogenicity risk
- fertility and early embryonic development risk, and
- the toxicity of a major human metabolite, M20, that was observed at negligible levels in previous animal studies.

2.2.2. Toxicology

The following studies were provided with this submission.

Table 1. New Nonclinical Toxicology Studies Conducted

Study Type and Duration	Route of Administration	Species	Compound Administered	Document ID
Repeat Dose Studies				
2-week mouse study	Oral gavage	Mouse	Abemaciclib	8001979
3-month mouse study	Oral gavage	Mouse	Abemaciclib	8002073
6-month rat study	Oral gavage	Rat	Abemaciclib and M20 (LSN3106726)*	8002603
Genotoxicity				
Micronucleus study	Oral gavage	Rat	M2 (LSN2839567)*	00353483
Micronucleus study	Oral gavage	Rat	M20 (LSN3106726)*	00353484
Carcinogenicity				
2-year study	Oral gavage	Rat	Abemaciclib	8002068
Reproductive and Developmental Toxicology Studies				
Male fertility study	Oral gavage	Rat	Abemaciclib	9001506
Female fertility and early embryonic development study	Oral gavage	Rat	Abemaciclib	9001507

*Major human metabolite of abemaciclib

Repeat dose toxicity

Repeat-dose toxicity studies were performed in mice in order to select doses for the ongoing 2 year carcinogenicity study.

A 6 month repeat-dose toxicity was performed in rats to support the new indication with long-term toxicity data and to qualify the main human metabolite M20 which is formed in less amounts in toxicity species.

2-Week Repeat-Dose Study in Mice

Administration of abemaciclib by once daily oral gavage at dose levels of 10, 50, or 150 mg/kg/day was generally well tolerated in CD-1 mice for a period of 14 days at levels up to 150 mg/kg/day. Slight changes were noted in mean body weight and food consumption mostly at 150 mg/kg/day. Minimal to moderate abemaciclib-related changes were observed in hematology and clinical chemistry parameters at greater than or equal to 10 mg/kg/day; most of these changes were likely secondary to the decrease in food consumption, and not adverse. Based on these results and in the absence of histopathology evaluation, the maximal tolerated dose (MTD) for this study was 150 mg/kg/day.

3- Month Repeat-Dose Study in Mice

Administration of abemaciclib to CD-1 mice by once daily oral gavage at dose levels of 5 and 30 mg/kg/day was well tolerated. At 150 mg/kg/day, the highest dose tested, abemaciclib resulted in preterminal deaths between Days 5 and 84 and consequential early termination of males and females by Day 85 due to adverse clinical findings. The primary abemaciclib related clinical findings at 150 mg/kg include one or more of the following: lower body weights, lower food consumption, decreased activity, abdominal distension, dehydration, cold to the touch, or, skin pallor.

In preterminal and terminal animals, the macroscopic and/or microscopic findings, with associated hematology and serum chemistry changes, were observed in bone marrow, lymphoid organs, gastrointestinal tract, reproductive organs, kidney, pancreas, liver, heart – vacuolation only, parathyroid gland, adrenal gland – vacuolation only, lung, and eye.

The alterations in hematology parameters, which are likely related to bone marrow effects, lymphoid organ effects, or both; and microscopic changes in the kidney, pancreas and eyes noted at 150 mg/kg/day were considered adverse based on the incidence and/or severity of the changes. Based on the overt toxicity observed at 150 mg/kg/day, the no observed adverse effect level (NOAEL) was 30 mg/kg/day.

6-Month Repeat-Dose Study in Rats

Administration of abemaciclib at 10 and 30 mg/kg/day to Sprague-Dawley rats, or M20 (LSN3106726), a major human metabolite of abemaciclib, at 20 mg/kg/day in male rats or 60 mg/kg/day in female rats by once daily oral gavage for 6 months resulted in marked body weight loss and decreased food consumption, with associated clinical signs of thin condition and prominent backbone at ≥ 10 mg/kg/day abemaciclib in males and females. Abemaciclib-related deaths or unscheduled euthanasia occurred in males dosed at 30 mg/kg/day. Test item-related findings were observed in: eyes, lungs, kidneys, heart, gastrointestinal tract, lymphoid tissues, bone marrow, several glands, and trachea.

The findings with M20 were similar to or less severe than findings with abemaciclib. Findings in the eye and lung were adverse. Due to the magnitude of changes and the nature of the microscopic findings, the no observed adverse effect level (NOAEL) for abemaciclib in males and females and M20 in males could not be established in this study. The NOAEL for M20 in females was 60 mg/kg/day.

For toxicokinetics see below.

Carcinogenicity

2-Year Carcinogenicity Study in Rats

Study design

Table 2. Study Design for Carcinogenicity Study in Rats

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Animal Numbers			
				Main Study		Toxicokinetic Study[a]	
				Males	Females	Males	Females
1	Reference Item	0	0	60	60	4	4
2	Abemaciclib	0.3	0.1	60	60	10	10
3	Abemaciclib	1	0.33	60	60	10	10
4	Abemaciclib	3	1.0	60	60	10	10
5	Health Screen[b]	–	–	10	10	–	–

Abbreviations: – = Not applicable; Conc. = Concentration.

[a] Toxicokinetic animals were used for toxicokinetic evaluation only. One animal/sex/group served as a replacement TK animal, when needed.

[b] Health Screen animals were used for health-screen evaluations only.

Mortality

The number of control male and female surviving rats decreased to 20 prior to the planned termination week (during Week 95 and 100, respectively). Therefore, terminal necropsies commenced on Day 659 (in Week 95) for males and Day 700 (in Week 100) for females.

Clinical observations

Clinical observations were noted at all dose levels in males. The observations were consistent with general toxicity and not indicative of any specific type of toxicity. There were no clinical observations in females.

Body weight and food consumption effects

Abemaciclib treatment caused decreased body weight gains at 1 mg/kg and above. There were no effects of abemaciclib treatment on food consumption in females; however, paradoxically, increased food consumption was observed in male rats at 1 mg/kg and above.

Neoplastic changes

Neoplastic changes were limited to benign interstitial (Leydig) cell tumours at the highest dose tested. These tumours were accompanied by interstitial cell hyperplasia at all dose levels tested. There were no increases in other types of neoplasms in male rats. There were no increases in any type of neoplasm in female rats.

Table 3. Treatment-Related Neoplasms and Related Non-Neoplastic Effects in Male Rats Treated with Abemaciclib

Group	1	2	3	4
Dose (mg/kg/day)	0	0.3	1	3
No. Animals per Group	60	60	60	60
Testis (No. Examined)	60	60	60	60
Interstitial (Leydig) cell adenoma[a]	(0)[b]	(1)	(1)	(7)*
Hyperplasia; interstitial (Leydig) cell	(2)	(4)	(9)	(16)
Minimal	2	4	8	6
Mild	0	0	0	9
Moderate	0	0	1	1

* Statistically significant increase in the overall trend test and pairwise comparison (P≤0.05; rats administered the reference item compared to rats administered 3 mg/kg/day of abemaciclib)

[a] Values in this row combine individual animals reported as having a single neoplasm with individuals reported as having multiple neoplasms.

[b] Numbers in parentheses represent the total number of animals with the finding.

Non-neoplastic effects

In addition to the neoplastic testicular effects, adverse effects in the testes and epididymis were observed at all dose levels. Minor clinical observations of small prostate and seminal vesicle also were noted.

Lens fiber degeneration and retinopathy were observed at all dose levels in male rats. These effects were observed at a much lower frequency and severity in female rats.

Dose-responsive renal tubular vacuolation and dilation occurred in rats treated with abemaciclib. Minimal to moderate urinary bladder inflammation was observed in high dose rats treated with abemaciclib. Transitional epithelium hyperplasia was secondary to this inflammatory effect.

A dose-responsive increase in vacuolated macrophages in the lungs was observed in rats treated with abemaciclib.

Dose-responsive atrophy of islets of Langerhans was observed in rats treated with abemaciclib. This finding could result in increased glucose concentration, which has been observed in other rat studies of abemaciclib but was not assessed in this study.

A dose-responsive increase in chief cell hypertrophy/hyperplasia was observed in rats treated with abemaciclib. Dose-responsive crypt hyperplasia was observed in all segments of the small intestine in rats treated with abemaciclib, along with gross observations of dilation or thick. While no microscopic findings were observed in the large intestine, gross observations of dilation or thick were also noted in some segments of the large intestine.

Dose responsive decreases in lymphoid cellularity were observed in lymph nodes GALT in rats treated with abemaciclib. Erythrophagocytosis was also observed in lymph nodes.

For toxicokinetics see below.

Reproduction toxicity

Fertility and early embryonic development study in female rats

Administration of abemaciclib to female Crl:CD(SD) Sprague Dawley rats by once daily oral gavage beginning 14 days before cohabitation, during cohabitation and continuing until Day 6 postcoitum at dose levels of 1, 4 and 20 mg/kg/day resulted in adverse effects on food consumption, body weight gain, and body weights at 20 mg/kg/day. There were no adverse effects on reproductive performance. Based on these results, the maternal no-observed-adverse- effect level (NOAEL) was 4 mg/kg/day and the NOAEL for fertility and early embryonic development was 20 mg/kg/day.

Fertility Study in Male Rats

The administration of abemaciclib by once daily oral gavage beginning 28 days prior to mating at dose levels of 1 and 10 mg/kg, during the 2-week cohabitation period, and continuing through the day before euthanasia, which was at least 50 consecutive doses, resulted in reduced food consumption and lower body weights at 10 mg/kg/day. There were no abemaciclib-related effects on any paternal fertility parameters assessed or on reproductive performance. Based on these results, the no-observed-adverse-effect level (NOAEL) for paternal toxicity was considered to be 1 mg/kg/day, and the no-observed-effect level (NOEL) for male reproductive function, mating and fertility, was 10 mg/kg/day.

Metabolite toxicity

The human metabolite M20, formed in limited amounts in toxicity species was included in the 6 month repeat-dose toxicity study.

The metabolites M2 and M20 were studied in the rat micronucleus assay. Administration of M2 (LSN2839567) by once daily oral gavage to Crl:CD(SD) rats at dose levels of 500, 1000, and 2000 mg/kg/day for 2 consecutive days resulted in a negative response for induction of bone marrow micronuclei. Administration of M20 (LSN3106726) by once daily oral gavage to Crl:CD(SD) rats at dose levels of 500, 1000, and 2000 mg/kg/day for 2 consecutive days resulted in a negative response for induction of bone marrow micronuclei. Additionally, M20-related mortality occurred in one male at 2000 mg/kg/day on Day 2 in the definitive study phase.

Toxicokinetic data

Exposure multiples for oral abemaciclib in the toxicity studies:

Table 4. Exposure Multiples for Oral Abemaciclib Based on Systemic Exposure

Species	Dose (mg/kg)		$AUC_{0\text{-}24hr}$ (ng•hr/mL)		Exposure Multiple[a]	
Human[b] (150 mg BID, 300 mg/day)			4180		--	
	Male	Female	Male	Female	Male	Female
Repeat-dose toxicity						
Mouse 3-month NOAEL[c]	30	30	7430	32900	1.8	7.9
Rat 6-month LOAEL[d]	10	10	12200	15900	2.9	3.8
Rat 6-month MTD[d]	30	30	31300	24700	7.5	5.9
Dog 3-month NOAEL[e]	ND	1	--	488	--	<1.0
Dog 3-month MTD[e]	3	3	1730	1400	<1.0	<1.0
Fertility						
Male rat NOEL[f]	10	--	12415	--	3.0	--
Female rat NOAEL[g]	--	20	--	19000	--	4.5
Embryo-fetal development						
Rat NOAEL[h]	--	1	--	843	--	<1.0
Carcinogenicity						
Rat NOAEL[i]	1	3	1000	5440	<1.0	1.3

Abbreviations: AUC = area under the plasma concentration x time curve; C_{max} = maximal plasma concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; MTD = maximum tolerated dose.

a Exposure multiple is the $AUC_{0\text{-}24hr}$ in animals/$AUC_{0\text{-}24hr}$ in humans.

b Geometric mean exposure of abemaciclib from monarchE at 150 mg BID. $AUC_{\tau,ss}$ in humans, where τ=12 hr, was doubled to estimate $AUC_{0\text{-}24hr}$ in humans.

c NOAEL determined in 3-month repeat-dose toxicity study (8002073); plasma toxicokinetics determined on Day 91.

d MTD and LOAEL determined in 6-month repeat-dose toxicity study (8002603); plasma toxicokinetics determined on Day 182. An NOAEL was not determined in this study.

e NOAEL determined in 3-month repeat-dose toxicity study (8000445); plasma toxicokinetics determined on Day 91. An NOAEL was not determined in male dogs.

f NOEL for reproductive effects determined in male fertility study (9001506); plasma toxicokinetics determined on Day 28 (803871).

g NOAEL for reproductive effects determined in female fertility study (9001507); plasma toxicokinetics determined on Gestation Day 6.

h NOAEL for reproductive effects determined in rat embryo-fetal development study (8299046); plasma toxicokinetics determined on Day 17.

i NOAEL determined in rat carcinogenicity study (8002068); plasma toxicokinetics determined on Day 182.

In the 6-month repeat-dose toxicity study in rats, the dose level of M20 used in male rats and the dose level of M20 used in female rats were selected in order to expose rats of both sexes to amounts of M20 similar to the exposure observed in patients treated with abemaciclib. Mean rat exposure was 91% of typical patient exposure at 150 mg abemaciclib given twice daily. While female rat exposure was only 48% of patient exposure, M20 effects were similar in male and female rats; thus, use of the average rat exposure is justified.

Table 5. M20 Exposure in Humans and Rats

	$AUC_{0\text{-}24hr}$ (ng•hr/mL)		
Species	Male	Female	Mean
Human-150mg BID[a]	–	–	3020
Rat-20 mg/kg (M) / 60 mg/kg (F)[b]	4040	1440	2740

Abbreviations: BID = twice daily; F = female; M = male.

a Geometric mean exposure from monarchE. $AUC_{\tau,ss}$ in humans, where τ=12 hr, was doubled to estimate $AUC_{0\text{-}24hr}$ in humans.

b Rat exposure on Day 182 of the 6-month repeat-dose rat study (Study 8002603).

Additional toxicity findings

Eye effects

On ophthalmic examination in a 6-month rat study, males treated with 10 mg/kg/day of abemaciclib had observed bilateral cataracts. At necropsy, clinical observations of eye opacity were seen in that group. These observations correlated with microscopic lens fiber degeneration, also known as cataracts.

Lens fiber degeneration was observed in male rats treated with abemaciclib for 6 months. It was not observed in female rats treated with abemaciclib. This degeneration was not dose responsive, and occurred at a greater frequency in male rats administered 10 mg/kg/day as compared with male rats administered 30 mg/kg/day. Male and female rats treated with 30 mg/kg/day of abemaciclib had test item-related changes including very faint, superficial and diffuse corneal opacities with no microscopic correlate.

In the 6-month study, male and female rats treated with 30 mg/kg/day of abemaciclib had the finding of pale fundus. A high number of these rats had concurrent microscopic finding of retinal atrophy. In the 2-year carcinogenicity study, vitreoretinopahy was observed in male rats at all dose levels and in female rats at only the high dose. In the 3-month study, retinal atrophy was also observed in mice, but only in 3 females at a dose the exceeded the MTD in mice. No eye effects were observed in dog studies or in rat studies less than 6 months in duration.

Heart valve effects

In a 6-month repeat-dose study in rats, administration of abemaciclib caused minimal heart valve effects. Vacuolated macrophages consistent with phospholipidosis and associated inflammation within heart valve leaflets were observed in rats treated with 30 mg/kg abemaciclib. This vacuolation was consistent with phospholipidosis that has been observed in previous studies in multiple cell types, including macrophages, lymphocytes and various epithelia. This was the first time vacuolated macrophages were observed in the heart valves and was accompanied by minimal, mixed cell inflammation in 3 of the 7 affected males. There was no evidence of myxomatous change, haemorrhage, or thickening and no clinical sequelae suggestive of decreased cardiac function. These heart effects were only observed at an abemaciclib-dose level that exceeded the MTD. No heart valve effects have been observed in

- shorter duration rat studies
- dog studies; however, the longest dog study that has been conducted is 3 months in duration, or
- the 2-year rat carcinogenicity study; however, the highest dose tested in that study was3 mg/kg.

Testicular interstitial cell tumours

In a rat carcinogenicity study, administration of abemaciclib resulted in an increased incidence of benign interstitial (Leydig) cell hyperplasia in rat testes at all dose levels tested and an increased incidence of interstitial cell adenoma at 3 mg/kg/day. These findings have not been observed in shorter-duration rat studies with abemaciclib, including the 6-month study.

2.2.3. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment has been conducted which assumes that patients will be dosed daily with abemaciclib at a maximum oral dose of 300 mg per day for both the authorized indication and the requested indication.

For the authorized indication, the maximum dose is 300 mg per day and the highest estimated regional disease prevalence in Europe is 0.0529%. The highest estimated regional disease prevalence in Europe for the requested indication is 0.0171% and the maximum dose is 300 mg per day. The maximum PEC of abemaciclib in the sewage treatment plant is 0.56 $\mu g \cdot L^{-1}$, in surface water is 0.030 $\mu g \cdot L^{-1}$, in ground water is 0.0060 $\mu g \cdot L^{-1}$, in sediment is 3.7 $mg \cdot kg^{-1}$, and in soil is 0.13 $mg \cdot kg^{-1}$.

For all indications, the predicted no-effect concentrations (PNECs) of abemaciclib for organisms associated with surface water, ground water, and the sewage treatment plant are 0.59, 2.0, and 100,000 $\mu g \cdot L^{-1}$, respectively. The PNECs of abemaciclib for organisms associated with sediment and soil are 78 and 8.2 $mg \cdot kg^{-1}$, respectively. The predicted environmental concentrations of abemaciclib are all lower than these PNEC values. Therefore, excretion of abemaciclib by humans is not expected to result in a significant environmental risk.

Table 6. Environmental risk assessment

Substance (INN/Invented Name): abemaciclib			
CAS-number: 1231929-97-7			
PBT Screening		**Result**	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD 107, 123	pH 4 = -0.32 pH 7 = 3.61 pH 9 = 4.22	log K_{ow} < 4.5 No bioaccumulation potential
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation - fish BCF	OECD 305	BCF_{KgL} = 289 to 383 $L \cdot kg^{-1}$	Not B
Persistence	OECD 308 DT50 at 12°C	Sediment (two river systems): - DT50 water: 5.1, 5.3 d - DT50 sediment: 42, 774 d - DT50 whole system: 114, 366 d Soil (4 soil systems): - DT50 soil: 1096 to 2629 d	vP
Toxicity	CMR	Toxicity to reproduction observed	T
PBT-statement	Abemaciclib is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	3.0	$\mu g \cdot L^{-1}$	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and environmental fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Soil: K_{Foc} = 1485432 L·kg^{-1} (soil 1) K_{Foc} = 242804 L·kg^{-1} (soil 2) K_{Foc} = 1947392 L·kg^{-1} (soil 3) Sludge 1: K_{oc} at 10 µg·L^{-1} = 80598 L·kg^{-1} K_{oc} at 1000 µg·L^{-1} = 20035 L·kg^{-1} Sludge 2: K_{oc} at 10 µg·L^{-1} = 17695 L·kg^{-1} K_{oc} at 1000 µg·L^{-1} = 8224 L·kg^{-1}	Soil: average K_{Foc} used in ERA, 1225209 L·kg^{-1} Sludge: Koc was dependent on concentration of abemaciclib. K_{oc} at low conc. used in ERA
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	OECD 308	System 1 at 12°C - DT50, water = 5.1 days - DT50, sediment = 774 days - DT50, whole system = 366 days - shifting to sediment = 98.8% System 2 at 12°C - DT50, water = 5.3 days - DT50, sediment = 42 days - DT50, whole system = 114 days - shifting to sediment = 96.8%	Two river system evaluated. Sediment risk assessment triggered

Phase IIa Effect Studies					
Study Type	**Test Protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	14 5.9	$\mu g \cdot L^{-1}$ $\mu g \cdot L^{-1}$	Growth rate Yield
Daphnia sp. Reproduction Test/*Daphnia magna*	OECD 211	NOEC	20	$\mu g \cdot L^{-1}$	Total length and reproduction
Fish, Early Life Stage Test/*Pimephales promelas*	OECD 210	NOEC	75	$\mu g \cdot L^{-1}$	Total length, wet weight, dry weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 1000000	$\mu g \cdot L^{-1}$	Heterotrophic, nitrification and total respiration
Phase IIb Effect Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	780	$mg \cdot kg^{-1}$	Emergence ratio, male development rate, normalized to 10% organic carbon
Sediment dwelling organism/*Lumbriculus variegatus*	OECD 225	NOEC	2806	$mg \cdot kg^{-1}$	Dry weight, normalized to 10% organic carbon
Sediment associated organism/*Hyalella azteca*	U.S. EPA 600/R-99/064	NOEC	≥5190	$mg \cdot kg^{-1}$	Survival, growth, reproduction, normalized to 10% organic carbon
Earthworm, Acute/*Eisenia fetida*	OECD 207	NOEC	82	$mg \cdot kg^{-1}$	Body weight changes, normalized to 10% organic carbon
Soil Microorganisms, nitrogen transformation	OECD 216	NOEC	1020	$mg \cdot kg^{-1}$	respiration, normalized to 2% organic carbon
Soil microorganisms, carbon transformation	OECD 217	NOEC	1020	$mg \cdot kg^{-1}$	respiration, normalized to 2% organic carbon
Most sensitive plant: Tomato, seedling emergence/*Solanum lycopersicum*	OECD 208	NOEC	322	$mg \cdot kg^{-1}$	Fresh shoot weight, normalized to 2% organic carbon
Collembola, reproduction/*Folsomia candida*	OECD 232	NOEC	≥ 669	$mg \cdot kg^{-1}$	Survival and reproduction, normalized to 2% organic carbon

2.2.4. Discussion on non-clinical aspects

To support the current application for an adjuvant indication in early breast cancer, the MAH has performed additional toxicology studies. This is in line with recommendations in the ICH S9 Q&A on the need for further nonclinical data when moving from advanced cancer to a less severe disease.

A chronic repeat-dose toxicity study was performed in rats. This study included groups of rats treated with the main human metabolite M20 which is formed in small amounts in toxicity species and therefore not qualified in previous toxicity studies. No safety concerns were identified for the metabolite M20 which was adequately qualified with this study.

The toxicity findings in the 6-month study with abemaciclib were to a large extent similar to what was previously seen in the 3-month repeat-dose toxicity study. However, there were novel toxicity findings

not previously seen. There were eye findings on cataract, corneal opacity, and retinopathy. There were also findings on retinopathy in a 2-month mouse repeat-dose toxicity study. The MAH considers the clinical relevance of these findings to be low. In an analysis of clinical data, a numerical imbalance in cataract was observed but it is stated that the rate was within the bounds of cataract incidence in the general population. The MAH will monitor cataract events as per standard safety surveillance procedures. Reference to the eye effects is made in section 5.3 of the SmPC. Even though in clinical studies eye problems did not seem to be a major problem, considering the fact that this concerns potentially serious and irreversible effects, such as retinopathy, that Verzenios is intended for long-term use and that there was no safety margin for these effects, the clinical relevance of the eye effects was further discussed, taking into account the potential mechanism behind these effects. The MAH provided, during this procedure, a cumulative review of available data on retinal toxicity in patients treated with abemaciclib across the clinical development program (cutoff date of 28 September 2020). This review provides no clear signal for a clinical relevance of the animal findings.

Heart valve effects, inflammation accompanied by vacuolated macrophages, was seen in rats at the highest dose. The likelihood of the new heart valve effects translating to humans is low. The MAH has not identified a safety signal of drug induced valvulopathy at the time the finding was identified in rats in patients treated with abemaciclib. As requested, the MAH has updated section 5.3 of the SmPC to include mentioning of heart valve effects. The MAH continues to monitor cardiac events as per standard safety surveillance procedures.

Abemaciclib was assessed for carcinogenicity in 2-year studies in rats and mice. In male rats, daily oral administration of abemaciclib resulted in benign testicular interstitial cell adenomas at exposures approximately 1.5 times human clinical exposure. In addition, interstitial cell hyperplasia was observed at exposures approximately 0.1 times human clinical exposure. It is unknown if these effects will translate to humans. There were no neoplastic findings in mice or in female rats that were due to administration of abemaciclib. These finding are mentioned in the SmPC section 5.3. The findings are not considered of importance for the benefit-risk assessment.

Because the mechanism of carcinogenicity for the abemaciclib-induced testicular effects is unknown at this time, the likelihood of abemaciclib-induced interstitial cell adenomas translating to humans is unknown. Rat interstitial cell hyperplasia and the continuum into interstitial cell tumours (ICTs) are generally not considered relevant to human health risk. Spontaneously occurring ICTs are common in rats but rarely arise in humans. A search of approved drugs identified at least 34 drugs that cause benign interstitial cell tumours in rats; however, this effect does not translate to humans for these drugs. These tumours in rats generally occur subsequent to persistently increased luteinizing hormone (LH) signaling, while persistent LH drive does not have similar effects in men. Humans with endocrine disorders in which LH is persistently high over the course of a lifetime, such as familial male precocious puberty, do not have increased occurrence of ICT. Plasma LH levels have not been evaluated in abemaciclib-treated rats; thus, the MAH currently has no data to determine if increases in LH are the cause of the ICT observed in this rat carcinogenicity study.

Abemaciclib may impair fertility in males of reproductive potential. In repeat-dose toxicity studies up to 3 months duration, abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These effects occurred in rats and dogs at exposures approximately 2 and 0.02 times human clinical exposure, respectively. In a rat male fertility study, abemaciclib had no effects on reproductive performance. In a rat female fertility and early embryonic development study and in repeat-dose toxicity studies, abemaciclib did not have any effect on

reproductive performance or any important effects on the female reproductive tract indicative of a risk of impaired fertility in females. These findings are reflected in sections 4.6 and 5.3 of the SmPC.

2.2.5. Conclusion on the non-clinical aspects

The findings of the new studies were generally consistent with the findings of previous studies with abemaciclib; however, some new findings were noted, in relation to eye effects, heart valve effects and testicular interstitial cell tumours, of low clinical relevance to humans. There are no objections to the approval of the new indication from a non-clinical point of view.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Table 7. Tabular overview of clinical studies

Study ID	Phase, Study design, control type	Population	Study Posology	Study Objective	Subjs by arm entered/ compl.
monarchE; I3Y-MC-JPCF	Phase 3, multicenter, randomized, open-label study of abemaciclib + ET versus ET alone as adjuvant treatment.	Patients (women, men) aged with confirmed HR+, HER2-negative (HER2-) early-stage resected invasive breast cancer without evidence of distant metastases at high risk of recurrence defined as ≥ 4 pALN (positive axillary lymph nodes), or 1-3 pALN and: tumour size ≥ 5 cm, histological grade 3, or Ki-67 ≥ 20 % (Cohort 2).	The A+ET arm: Endocrine therapy (standard of care) + abemaciclib 150 mg BID PO The ET only arm: Endocrine therapy (standard of care). Patients were randomized to Arms 1 and 2 in 1:1 ratio for both Cohorts 1 and 2.[a]	Primary objective: To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2-, early-stage breast cancer for abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone.	Planned: 4580 Entered: 7372 Randomized: 5637 Treated: 5591 Cohort 1: Abemaciclib +ET: 2555 ET: 2565 Cohort 2: Abemaciclib +ET: 253 ET: 264

[a]Cohort 1: Those with at least 1 positive node and eligible based on clinical pathological features (degree of axillary lymph node involvement, tumour size, and/or grade) regardless of Ki-67 status. Cohort 2: Those with at least 1 positive node and eligible exclusively based on central Ki-67 status. These patients would not be eligible based on degree of axillary lymph node involvement, tumour size, and/or histologic grade.

2.3.2. Pharmacokinetics

The MAH has provided a popPK analysis to support that exposure is similar in patients with early breast cancer and patients with advanced or metastatic breast cancer.

PK background

In the therapeutic dose range of 50-200 mg, the increase in AUC and C_{max} is approximately dose proportional. Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolised to several metabolites primarily by CYP3A4. The mean plasma elimination half-life for abemaciclib in patients was 24.8 hours.

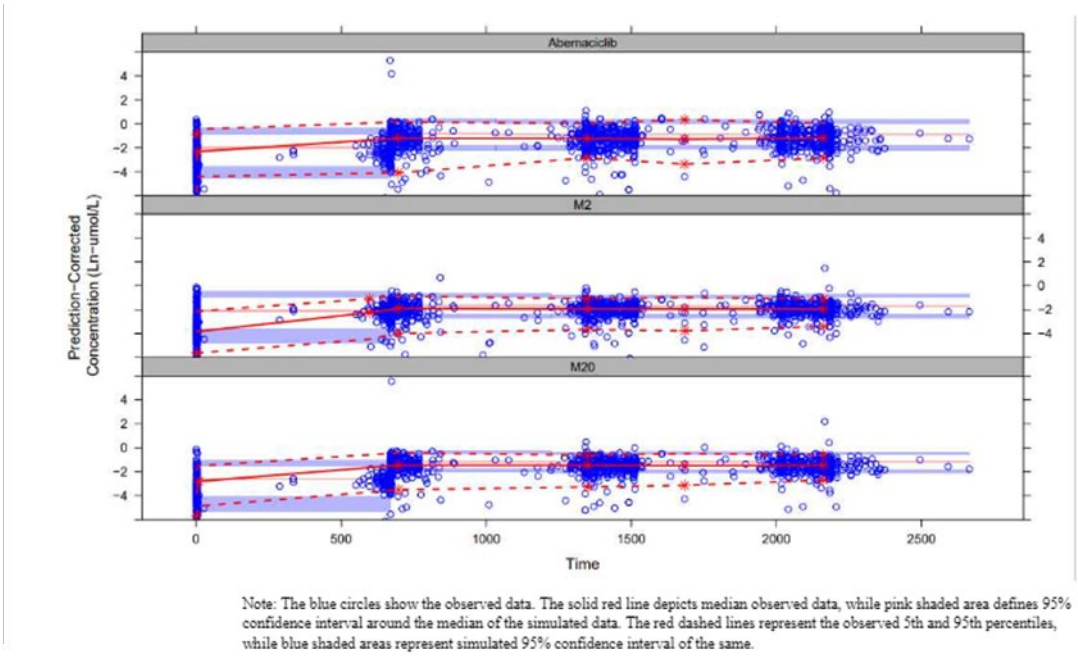
popPK analysis

Pharmacokinetic samples were collected in approximately 20% of patients receiving abemaciclib plus ET. A total of 4 PK samples were collected in these patients over a period of 3 months. The actual time and date of the PK sample was recorded. Plasma samples obtained during the study were analysed for abemaciclib and metabolites M2 and M20.

The abemaciclib mechanistic PopPK model, which was previously developed using a dataset of 12 clinical studies including MONARCH 2 was used to analyse the monarchE PK data for abemaciclib, M2, and M20. A total of 500 model simulations were performed using previous model. Simulated and

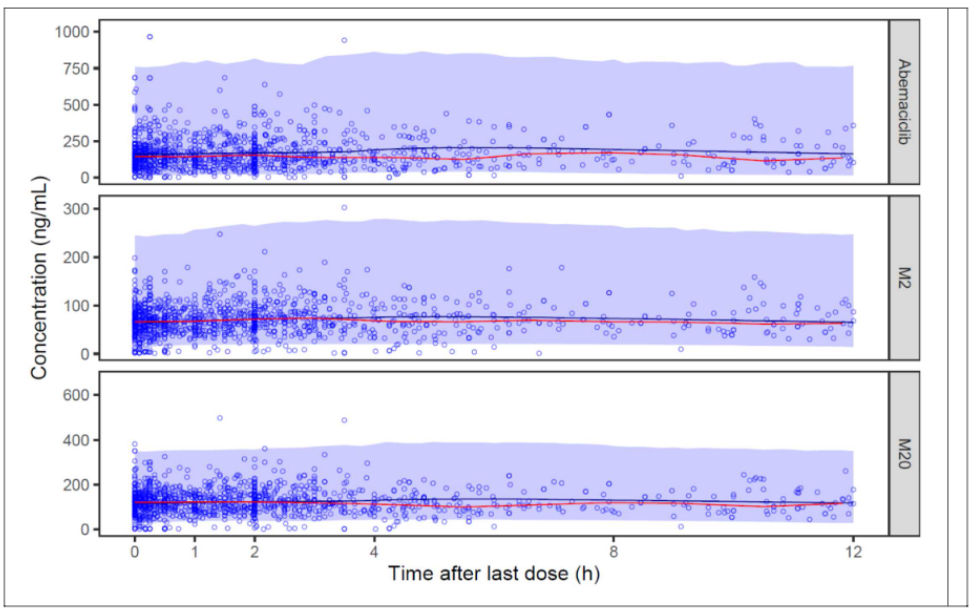
observed distributions were compared in pcVPCs and VPCs. The simulated steady-state exposures for abemaciclib, M2, and M20 and the total active species in monarchE are summarized in Table 8. When comparing the monarchE PK results to the MBC Phase 3 clinical study MONARCH3, the PK exposures appear to be slightly lower in monarchE (Table 9). One possible explanation could be the difference in disease burden between the 2 patient populations. Metastatic disease has been linked to high levels of inflammation, which in turn is associated with suppressed activity of drug-metabolizing enzymes such as CYP3A4.

Figure 1. Prediction-corrected visual predictive check for log abemaciclib versus time after the first dose (days) in monarchE



Note: The blue circles show the observed data. The solid red line depicts median observed data, while pink shaded area defines 95% confidence interval around the median of the simulated data. The red dashed lines represent the observed 5th and 95th percentiles, while blue shaded areas represent simulated 95% confidence interval of the same.

Figure 2. Visual predictive check for abemaciclib versus time after the first dose (days) for the first 12 hours postdose at steady-state in monarchE using average dose



Note: The blue circles show the observed data for Visit 2 onwards. The red line depicts median observed data. The blue line and shaded area represent the median and 95% confidence interval of the simulated steady-state data using the average dose for the duration of the study.

Table 8. Summary of Simulated Steady State Exposures for Abemaciclib, M2, M20, and Total Active Species in monarchE

Exposure [a,b,c]	Geometric mean (%CV) [c]			
	Abemaciclib (ng/mL)	**M2 (ng/mL)**	**M20 (ng/mL)**	**Total active species (µmol/L)**
$C_{min,ss}$	143 (110)	62.6 (67)	113 (58)	0.688 (58)
$C_{max,ss}$	211 (79)	77.4 (61)	137 (54)	0.903 (50)
	Abemaciclib (ng·h/mL)	**M2 (ng·h/mL)**	**M20 (ng·h/mL)**	**Total active species (µmol·h/L)**
$AUC_{\tau,ss}$	2090 (84)	854 (61)	1510 (52)	9.53 (49)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{min,ss}$ = minimum/trough concentration at steady state; CV = coefficient of variation.

a Values are summarized using individual exposure metrics obtained from the population estimates.

b Exposure estimates are based on individual average doses averaged over time (the average of the individual averaged doses was 130 mg).

c N = 483.

Table 9. Comparison of PK for monarchE and MONARCH 3

Exposure[a]	Geometric mean (%CV)[c]			
	monarchE[b,c]	**MONARCH 3[d,e]**	**monarchE[b,c]**	**MONARCH 3[d,e]**
	Abemaciclib (ng/mL)		**Total active species (µmol/L)**	
$C_{min,ss}$	143 (110)	181 (47)	0.688 (58)	0.820 (54)
$C_{max,ss}$	211 (79)	249 (42)	0.903 (50)	1.02 (48)
	Abemaciclib (ng·h/mL)		**Total active species (µmol·h/L)**	
$AUC_{\tau,ss}$	2090 (84)	2540 (42)	9.53 (49)	11.0 (49)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{min,ss}$ = minimum/trough concentration at steady state; %CV = percent coefficient of variation; PK = pharmacokinetics.

a Values are summarized using individual exposure metrics obtained from the population estimates.

b Exposure estimates are based on individual average doses averaged over time (the average of the individual averaged doses was 130 mg).

c N=483.

d Exposure estimates are based on individual average doses averaged over time (the average of the individual averaged doses was 132 mg).

e N=322.

2.3.3. PK/PD modelling

Exposure-response analyses were conducted to assess the relationships between abemaciclib exposures and safety endpoints in monarchE, specifically the two most frequent treatment-emergent adverse events, neutropenia and diarrhoea. The predicted probability of diarrhoea at any time was 75% for patients receiving abemaciclib plus ET, 93% for patients receiving opioids in addition to abemaciclib plus ET, and 6% for patients receiving ET alone. The model predicts ≥Grade 3 neutropenia in 9% (95% CI: 6.4, 11.0) of monarchE patients at the nadir (28 – 43 days after start of abemaciclib treatment).

2.3.4. Discussion on clinical pharmacology

No difference in PK between patients with early breast cancer and patients with advanced or metastatic breast cancer is expected, which was supported by a popPK report. A previous popPK model was used, without re-estimating parameters. VPCs indicate that exposure is similar in patients with

early breast cancer and patients with advanced or metastatic breast cancer. The pcVPCs are small and difficult to interpret but indicate some over-prediction. The popPK model has previously been assessed and has some limitations, it is however agreed that the provided VPC indicate similar PK. A slightly lower exposure was reported in monarchE compared to Monarch 3 however this difference is not considered significant and no change to section 5.2 of the SmPC is required.

The exposure-safety analysis confirms previous findings which are managed with dose adjustments for safety and tolerability.

2.3.5. Conclusions on clinical pharmacology

Overall, based on the updated data submitted by the MAH which included a popPK analysis, no difference in PK is expected in the new patient population. Thus, the MAHs proposal not to update section 5.2 in the SmPC is accepted.

2.4. Clinical efficacy

2.4.1. Main study

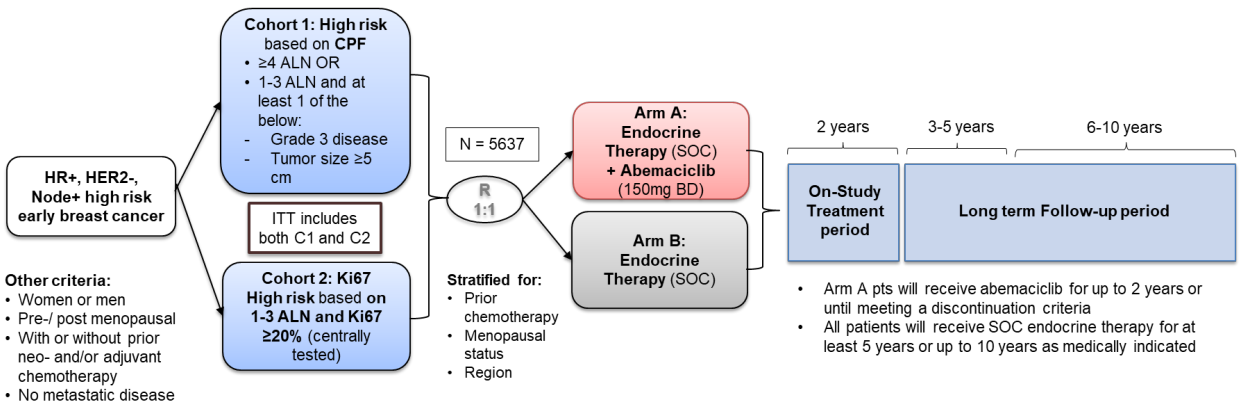
Title of Study

monarchE

A Phase 3, global, randomized, open label study of abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, HR+, HER2-, breast cancer (I3Y-MC-JPCF).

Methods

Figure 3. monarchE study design



Abbreviations: ALN = axillary lymph nodes; BD = twice daily; C = cohort; CPF = clinical pathological features; HER2 = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor-positive; ITT = intent to treat; Ki-67 = prognostic parameter; pts = patients; R = randomization; SOC = standard of care.

Study participants

Key inclusion criteria

- Female (regardless of menopausal status) or male ≥18 years of age

- The patient has confirmed HR+ (by local testing on primary disease specimen, tumour must be ER or PgR positive defined by immunohistochemistry (IHC) defined by immunohistochemistry (IHC) according to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP)), HER2-negative (HER2-, by local testing on primary disease specimen according to ASCO/CAP), early stage resected invasive breast cancer without evidence of distant metastases. Patients with bilateral breast cancer (diagnosis of invasive tumours in both breasts simultaneously or within 6 months of each other) can be eligible if all lesions tested on both sides are HR+/HER2- and adequate surgery has been performed in both breasts.
- The patient must have undergone definitive surgery of the primary breast tumour(s). The margins of the resected specimen must be histologically free of invasive tumour and /or a component of ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumour at the line of resection, additional excisions may be performed to obtain clear margins. If tumour is still present at the resected margin after re-excision(s), the patient must undergo mastectomy to be eligible. Of note, patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.
    - For patients who undergo mastectomy or wide local excision where deep margin abuts the pectoralis fascia, patients with microscopic positive margins are eligible as long as radiotherapy of the chest wall is administered prior to study entry. Patients with positive anterior margins may be eligible if there is no gross disease left behind (radiotherapy as per local guidelines).
    - Where surgical excision of supraclavicular or internal mammary nodes is not feasible, residual nodes should be irradiated in accordance with standard guidelines.
    - If given, radiation therapy (for example, post-mastectomy or post-lumpectomy) should be administered according to standard guidelines.
- The patient must have tumour tissue from breast (preferred) or lymph node for exploratory biomarker analysis available prior to randomization.
- Patients must be node positive (microscopic and macroscopic tumour involvement are allowed; ipsilateral internal mammary and supraclavicular lymph nodes are allowed, but will not count toward the number of positive lymph nodes) and fulfil one of the following criteria:
    - Pathological tumour involvement in ≥4 ipsilateral axillary lymph nodes.

      OR
    - Pathological tumour involvement in 1 to 3 ipsilateral axillary lymph node(s) (for patients who received neoadjuvant therapy also cytological tumour involvement at time of initial diagnosis is allowed) and meet at least 1 of the following criteria:
        - Grade 3 as defined by a combined score of at least 8 points per the modified Bloom-Richardson grading system (Elston and Ellis 1991), also known as the Nottingham scale, or equivalent following discussion with the MAH CRP/CRS
        - pathological primary invasive tumour size ≥5 cm (for patients who received neoadjuvant therapy primary tumour size ≥5 cm on breast imaging is allowed). Note: if tumour size is needed to meet eligibility criteria, patients with multifocal/multicentric tumours may be eligible based on the addition of diameters of the individual lesions following discussion with the MAH CRP/CRS.

- Ki-67 index of ≥20% (for cohort 2) on untreated breast tissue as determined by the investigational assay at the Study JPCF central laboratory.

- The patient must be randomized within 16 months from the time of definitive breast cancer surgery.
- If the patient is currently receiving or initiating standard adjuvant endocrine therapy at time of study entry, she/he may receive up to 12 weeks of endocrine therapy until randomization following the last non-endocrine therapy (surgery, chemotherapy, or radiation), whichever is last. Use of GnRH analogues for ovarian suppression is not considered endocrine therapy for the purposes of this criterion. Note: Adjuvant treatment with fulvestrant is not allowed.
- Patients who received or will be receiving adjuvant chemotherapy must have completed adjuvant chemotherapy prior to randomization and patients must have recovered (Common Terminology Criteria for Adverse Events[CTCAE] Grade≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomization. Patients who are not candidates for adjuvant chemotherapy or decline chemotherapy are permitted. Patients may also have received neoadjuvant chemotherapy. A washout period of at least 21 days is required between last adjuvant chemotherapy dose and randomization (provided the patient did not receive radiotherapy).
- Patients who received or will be receiving adjuvant radiotherapy must have completed radiotherapy prior to randomization, and patients must have recovered (Grade ≤1) from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization.
- Women of reproductive potential must have a negative blood pregnancy test at baseline (within 14 days prior to randomization) and agree to use highly effective contraceptive methods to prevent pregnancy during the study and for 12 weeks following the last dose of study treatment. Males must agree to use an acceptable method of birth control and to not donate sperm during the study and for at least 12 weeks following the last dose of study treatment.
- ECOG PS≤1
- The patient has adequate organ function for all of the following criteria, defined as Hematologic: ANC ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, haemoglobin ≥8 g/dL. Hepatic: Total bilirubin ≤1.5 × ULN, ALT and AST ≤3 × ULN.

<u>Key exclusion criteria</u>

- The patient has metastatic disease (including contralateral axillary lymph nodes) or lymph node-negative breast cancer. Patients with inflammatory breast cancer are excluded. Inflammatory carcinoma should not apply to a patient with neglected locally advanced breast cancer presenting late in the course of their disease.
- Patients with a history of previous breast cancer are excluded, with the exception of ipsilateral DCIS treated by locoregional therapy alone ≥5 years ago. Patients with a history of contralateral DCIS treated by local regional therapy at any time may be eligible. Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix), unless in complete remission with no therapy for a minimum of 5 years from the date of randomization are excluded. For patients with a history of other non-breast cancers within 5 years from the date of randomization and considered of very low risk of recurrence per

investigator's judgment (for example, papillary thyroid cancer treated with surgery), eligibility is to be discussed with the MAH CRP/CRS.

- The patient has previously received treatment with any CDK4 and CDK6 inhibitor.
- The patient is receiving concurrent exogenous reproductive hormone therapy (for example, birth control pills, hormone replacement therapy, or megestrol acetate). Appropriate washout period between last dose of exogenous hormone therapy and randomization is up to the investigator's medical judgment (for example, applying 5 times the half-life elimination rule). Note: topical vaginal oestrogen therapy is permitted if all other non-hormonal options are exhausted.
- The patient has previously received endocrine therapy for breast cancer prevention (tamoxifen or aromatase inhibitors) or raloxifene.
- The patient has serious pre-existing medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, [for example, estimated creatinine clearance <30mL/min],interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or pre-existing Crohn's disease or ulcerative colitis or a pre-existing chronic condition resulting in clinically significant diarrhoea).
- The patient has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible. Any patient with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded. Patients with a history of venous catheter occlusion by thrombus that did NOT surround the catheter, and the lumen could be made patent by appropriate measures (for example, saline or thrombolytic agent), are not excluded.
- The patient has active systemic infections (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, or detectable viral infection requiring systemic therapy) or viral load (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrolment.

The eligibility criteria are considered acceptable.

Treatments

In both arms A and B, Day 1 of on-study treatment period was defined by the first dose of treatment following randomization, i.e. abemaciclib and/or endocrine therapy (in the A+ET arm) or endocrine therapy (in the ET only arm), regardless if the patient was already receiving endocrine therapy prior to randomization. The first dose of abemaciclib and/or endocrine therapy was to be taken no later than 3 days after randomization.

Table 10. Study interventions administered

Arm	Abemaciclib	Standard Adjuvant Endocrine Therapy	On Study Treatment Period (Years 1-2)
A	150 mg twice daily, with at least 6 hours separating doses	Standard adjuvant ET of physician's choice	Treatment with abemaciclib was given for up to 2 years or until discontinuation criteria were met. In both arms, treatment with ET was given until discontinuation criteria were met.[a]
B	Not applicable	Standard adjuvant ET of physician's choice	

Abbreviations: GnRH = gonadotropin-releasing hormone; ET = endocrine therapy.

[a]Standard ET, per physician's choice such asletrozole, anastrozole, exemestane or tamoxifen with or without GnRH agonist, was taken as prescribed during the on-study treatment period (Years 1-2). In Year 3 and beyond, continued standard adjuvant ET to complete at least 5 years, if this was medically appropriate.
Source: Table JPCF.3.2. p 38 JPCF-04-body.pdf

Abemaciclib was administered as 50 mg capsules or tablets for oral administration.

The investigator was referred to the product label for administration of standard-of-care endocrine therapy of choice. A switch to another standard endocrine therapy was allowed as per the investigator's discretion only in the absence of an IDFS event, during the on-study treatment period. Adjuvant treatment with fulvestrant was not allowed at any time during the study. Concurrent treatment with SOC bone-modifying agents, such as bisphosphonates and denosumab, was permitted during treatment.

Table 11 summarizes a guidance for management of treatment-emergent, related, and clinically significant AEs of abemaciclib. If an investigator would like to suspend or reduce doses without one of the criteria below being met, this was acceptable and would not be considered a protocol deviation.

Table 11. Abemaciclib Dose Adjustments for Treatment-Emergent, Related, and Clinically Significant Adverse Events*

* Related means there is a reasonable causal relationship with abemaciclib.
Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ILD = interstitial lung disease.

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose reduction is NOT required.
Hematologic Toxicity	Recurrent[a] Grade 3 or Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity: **If patient requires administration of blood cell growth factors**	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.
Non-hematologic Toxicity[b] (except diarrhea, ALT/AST increased, ILD/pneumonitis and VTE[d])	Persistent or recurrent[a] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is NOT required.
Diarrhea	Persistent or recurrent[a] Grade 2 that does not resolve with maximal supportive measures, or requires hospitalization, or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5.0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Grade 4 (>20.0×ULN)	Abemaciclib therapy **MUST** be discontinued.	Abemaciclib therapy **MUST** be discontinued.
ALT/AST Increased	Elevation in AST and/or ALT >3 x ULN with total bilirubin >2 x ULN, in the absence of cholestasis	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued.
ILD/pneumonitis	Grade 2	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ILD/pneumonitis	Grade 3 or Grade 4	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued.

[a]Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- The patient showed stable hematological counts (Grade ≤2) during that timeframe
- In the absence of any infectious sign or risk factor
- The patient is benefiting from study treatment

[b]Additional guidance for renal and hepatic monitoring is in Section 9.4 JPCF-05-Protocols and Amendments.pdf .[c]Grade 3 ALT/AST increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 9.4 JPCF-05-Protocols and Amendments.pdf for additional guidance for hepatic monitoring.[d]For VTE, dose reduction of abemaciclib will be at the discretion of the investigator.

Source: Table JPCF.7.2. p. 39-40 JPCF-05-Protocols and Amendments.pdf

Dose adjustments as outlined in Table 11 were allowed. Abemaciclib was to be reduced sequentially by 1 dose level. If a patient receiving the 50-mg twice daily dose of abemaciclib required further dose reduction, the patient must be discontinued from abemaciclib.

Table 12. Dose adjustments of abemaciclib

Dose Adjustment	Oral Dose	Frequency
0	150 mg	Twice daily with at least 6 hours between doses
1	100 mg	Twice daily with at least 6 hours between doses
2	50 mg	Twice daily with at least 6 hours between doses

Source: Table JPCF.7.3 p 42 JPCF-05-Protocols and Amendments.pdf

For patients requiring dose reduction(s), any re-escalation to a prior dose level was permitted only after consultation with the MAH CRP/CRS. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient was currently receiving.

Dose adjustment for endocrine therapy (on-study treatment period and beyond) was determined by the investigator and when applicable. For the A+ET arm, in the event that endocrine therapy was permanently discontinued for any reason other than an IDFS event per STEEP criteria, a patient should continue to receive abemaciclib. A switch to another endocrine therapy was permitted per physician's choice as part of standard of care. In the event that abemaciclib must be discontinued, a patient may continue to receive endocrine therapy per the investigator's clinical judgment.

Study treatment could be held up to 28 days to permit sufficient time for recovery from the toxicity.

Supportive care

Diarrhoea:

At randomization, patients in the A+ET arm should have received instructions on the management of diarrhoea. Patients should have been prescribed antidiarrhoeal therapy (for example, loperamide) on Visit 1.

In the event of diarrhoea, provided antidiarrhoeal therapy should have been initiated as early as possible. At the first sign of loose stools, the patient should have initiated antidiarrhoeal therapy, if not already receiving such therapy (for example, loperamide), and notified the investigator/site for further instructions and appropriate follow-up. If diarrhoea did not resolve with antidiarrhoeal therapy within 24 hours to either baseline or Grade 1, study drug was to be suspended until diarrhoea was resolved to baseline or Grade 1. When abemaciclib recommences, dosing was to be adjusted as outlined in Table 11. In cases of significant diarrhoea, Grade 2 through 4, which did not respond to interventions as outlined above, if the investigators were considering the addition of steroids to treat potential colitis, the sponsor strongly recommended an endoscopic procedure to document colitis prior to initiating steroids.

- In severe cases of diarrhoea, the measuring of neutrophil counts and body temperature was to be considered.
- If diarrhoea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones was to be prescribed.
- Patients with severe diarrhoea or any grade of diarrhoea associated with severe nausea or vomiting was to be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement.

Febrile neutropenia:

Patients experienced febrile neutropenia, especially with diarrhoea or dyspnoea, should have be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Events that require a patient to be hospitalized were considered SAEs.

Growth factor therapy:

Growth factors could not be administered to a patient to satisfy study inclusion criteria.

Growth factors was be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib was to be suspended if the administration of growth factors was required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced by 1 dose level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors had not already occurred.

Objectives

Primary objective:

To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer for abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone in the ITT population including both Cohort 1 and Cohort 2.

Secondary objectives:

- To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer with pre-treatment Ki-67 index ≥20% by central lab (from both Cohort 1 and 2)
- To evaluate the efficacy of abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone in terms of DRFS and OS.
- To assess the safety profile of abemaciclib plus adjuvant endocrine therapy compared to adjuvant endocrine therapy alone.
- To evaluate the relationship between abemaciclib, exposure and clinical (efficacy and safety) outcomes.
- To evaluate abemaciclib plus adjuvant endocrine therapy, versus adjuvant endocrine therapy alone, in terms of general oncology and breast cancer self-reported health-related quality of life (FACT-B 37 -item questionnaire), endocrine therapy-specific symptoms (the FACT-ES 19-item subscale and 2 FACIT-sourced items of cognitive symptoms and 3 FACIT-sourced items for bladder symptoms), and fatigue experienced during abemaciclib and/or endocrine therapy (the FACIT-F 13-item subscale).
- To evaluate health status to inform decision modelling for health economic evaluation using the EQ-5D-5L.

<u>Exploratory:</u>

- Assess the relationship between biomarkers and clinical outcome.
- Compare the prognostic significance (in terms of IDFS) of Ki-67 in pre- versus post-neoadjuvant therapy samples as assessed by central laboratory

Outcomes/endpoints

Table 13. Definitions for monarchE endpoints

Endpoint	Invasive Ipsilateral Breast Tumor Recurrence	Local/Regional Invasive Recurrence	Distant Recurrence	Death from Any Cause	Invasive Contralateral Breast Cancer[a]	Second Primary Non-Breast Invasive Cancer[b]
Overall survival[d]				X		
Invasive disease-free survival[d]	X	X	X	X	X	X
Distant relapse-free survival[d]			X	X		
Confirmation requirements[c]	Biopsy	Biopsy/FNA	Biopsy/FNA or imaging		Biopsy	Biopsy/FNA or imaging

Abbreviations: DCIS = ductal carcinoma in situ; FNA = fine needle aspiration; LCIS = lobular carcinoma in situ.
[a]The term "contralateral invasive breast cancer" is preferred to "second primary breast cancer" as it is less ambiguous. Ipsilateral invasive breast cancers are presumed to be a recurrence.
[b]This excludes squamous or basal cell skin cancers or new in situ carcinomas of any site like ipsilateral or contralateral DCIS/LCIS.
[c]If bone is the only site of disease, imaging must be performed to confirm recurrence.
[d]Hudis et al. 2007.
Source: Table APP.10.1, p 87, I3Y-MC-JPCF(e) Clinical Protocol.

Invasive disease-free survival (IDFS)

IDFS as defined by the STEEP System (Hudis et al. 2007). Invasive disease-free survival time is measured from the date of randomization to the date of first occurrence of:

- Ipsilateral invasive breast tumour recurrence
- regional invasive breast cancer recurrence
- distant recurrence
- death attributable to any cause
- contralateral invasive breast cancer
- second primary non-breast invasive cancer.

Recurrence of non-invasive breast cancer was not counted as an event.

Patients for whom no event has been observed will be censored on the day of their last assessment for recurrence or date of randomization if no post-baseline assessment for recurrence occurred. The detailed censoring rules are described in Table 14.

Table 14. Censoring rules for IDFS

Situation	Date of Event or Censor	Event / Censor
IDFS event	Date of earliest IDFS event	Event
No IDFS event	Date of last assessment for recurrence	Censored
Unless		
No post-baseline disease recurrence assessment	Date of randomization	Censored
IDFS event documented after more than 12 months (+ 28 days)* following the last disease recurrence assessment or randomization (whichever is later)	Date of last assessment for recurrence prior to the documented IDFS event, or date of randomization (whichever is later)	Censored

*12 months (+28 days) is the longest allowed interval between visits in long-term follow up period after Year 5 defined by the schedule of activities

A sequential gate-keeping strategy was utilized to control the family-wise type I error at 0.025 (one-sided) for IDFS in ITT, Ki-67 high (KI67H) and Cohort 1 Ki-67 high (C1-KI67H) populations. That is, IDFS was tested hierarchically in the order of ITT, KI67H, then C1-KI67H populations, each gated after the former population.

IDFS in Cohort 1 Ki-67 low (C1-KI67L) and Cohort 2 (C2) populations were tested as exploratory efficacy analyses.

Subgroup analyses of IDFS were performed for each of following potential prognostic subgroup variables:

- All baseline stratification factors
- Primary tumour size by pathology following definitive surgery
- Number of involved axillary lymph nodes
- Tumour stage
- Tumour grade
- Progesterone receptor status
- Age
- Race

Overall survival

The OS time was measured from the date of randomization to the date of death from any cause. For each patient who was not known to have died as of the data-inclusion cut-off date for a particular analysis, OS was censored for that analysis at the date of last contact prior to the data inclusion cut-off date.

A sequential gate-keeping strategy was utilized to control the overall type I error at 0.025 (one-sided) for the secondary endpoint OS in all randomized patients in Cohort 1 and Cohort 2. That is, OS was tested only if IDFS in ITT, KI67H, C1-KI67H populations were all significant.

Final OS analysis: 650 OS events or 10 years after last patient randomized, whichever occurred earlier.

Distant relapse free survival (DRFS)

Distance relapse free survival (DRFS) was measured from the date of randomization to the date of first occurrence of:

- Distant recurrence
- Death attributable to any cause

Patients for whom no event had been observed were censored at the day of their last assessment for disease recurrence or date of randomization if no post baseline disease recurrence assessment occurred. Distance relapse free survival events documented prior to the randomization date were censored at the date of randomization. Distance relapse free survival events documented after more than 12 months (+28 days) following the last disease recurrence assessment or randomization were censored at the last assessment for disease recurrence prior to the documented DRFS event, or date of randomization, whichever was later.

Health outcomes/Quality-of-life analyses

Patient reported outcomes are measured through paper versions of the following:

- Functional Assessment of Cancer Therapy - Breast (FACT-B)
- Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)
- Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES), 2 FACIT sourced items of cognitive symptoms (items HI9 and M9), and 3 FACIT-sourced items (items BL1, BL2 and P8) for bladder symptoms

All the FACT/FACIT questionnaires, subscales, and items are scaled using a 5-point Likert rating ranging from 0 'not at all' through 4 'very much.' The recall period is the past 7 days. For each instrument, percentage compliance was calculated as the number of completed assessments divided by the number of expected assessments (ie, patients still on study). Percentage compliance was summarized by treatment groups at each assessment visit and overall. Reasons for noncompliance were summarized.

A mixed effect, repeated measures model was applied to compare treatment arms by assessment with respect to each subscale and item score. The models included baseline score as a covariate and an unstructured covariance matrix was utilized. For each of the subscales and item scores, the analysis included all visits for which at least 25% of patients in each arm have an assessment. In the absence of published data on the minimally important difference of changes in the summary scores in the population of patients with EBC, an effect size of one-half standard deviation (0.5 SD) was used to represent an estimate of a minimally important difference (MID).

The EQ-5D-5L questionnaire was used to evaluate patients' health status to inform decision modelling for health economic evaluation.

Sample size

The study was powered to approximately 85% assuming an IDFS hazard ratio of 0.73 at a cumulative 1-sided alpha of 0.025. This requires approximately 390 events from across Cohort 1 and Cohort 2 by the time of the primary analysis after accounting for the interim efficacy and futility analyses. The number of patients required to observe approximately 390 events was calculated using Cytel East 6 and the following additional assumptions about pooled population in the two cohorts:

- Patients will enrol at a rate of 2, 8, 32 , 60 , 102, 140 , 164 , 188 , 198 , 206 , 218 , 238, 256, 260/month for the first 14 months, respectively, and then kept at 276/month for the remainder of the enrolment period.
- The time from first patient randomized to the observation of approximately 390 events will be approximately 4 years under the alternative hypothesis (hazard ratio of 0.73).
- The probability of a patient dropping out over the first 5 years following randomization is 10%.
- The 5-year IDFS rate for the control arm is 82.5%.

Under these assumptions, 4580 patients were to be enrolled.

Randomisation

Patients were randomized in a 1:1 ratio using an interactive web-response system (IWRS), to either up to 2 years of abemaciclib plus ET (the A+ET arm) or ET alone (the ET only arm) using the stratification factors:

- Prior treatment: neoadjuvant chemotherapy vs adjuvant chemotherapy vs no chemotherapy
- Menopausal status: premenopausal vs postmenopausal (menopausal status to be determined by investigator and based upon the patient's status at the time of diagnosis)
- Region: North America/Europe vs Asia vs Other

If a patient received both neoadjuvant and adjuvant chemotherapy, the patient will be stratified as neoadjuvant chemotherapy. Male patients will be stratified as postmenopausal at the time of randomization.

Blinding (masking)

MonarchE was a randomized, open-label study. Due to toxicities and laboratory abnormalities related to abemaciclib treatment, such as diarrhoea, neutropenia, and creatinine increase the open-label design was chosen. The sponsor was blinded to treatment group assignments until the study reached a positive outcome but not the patient or investigative site. An IDMC was responsible for reviewing the unblinded safety and efficacy analyses. The sponsor and all investigative sites will remain blinded to treatment group assignments for the aggregate database until the database lock for the final analysis.

In order to maintain the scientific integrity of this trial, access to study data will be strictly controlled prior to the interim and final analyses. Access to the electronic data capture (eDC) system will be limited to those who require this information for their role and all access will be documented.

Statistical methods

Analysis populations

Intent-to- Treat (ITT) population: will include all randomized patients in Cohort 1 and Cohort 2. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for baseline, efficacy, and health economics analyses.

Safety or Randomized and Treated (RT) population: will include all randomized patients in Cohort 1 and Cohort 2 who received any quantity of study treatment. The safety evaluation will be performed

based on the study regimen a patient actually received, regardless of the arm to which he or she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Ki-67 High (KI67H) population: will include all randomized patients in Cohort 1 and Cohort 2 with a centrally assessed Ki-67 index ≥20%.

Cohort 1 Ki-67 High (C1-KI67H) population: will include all randomized patients in Cohort 1 with a centrally assessed Ki-67 index ≥20%.

Cohort 1 Ki-67 Low (C1-KI67L) population: will include all randomized patients in Cohort 1 with a centrally assessed Ki-67 index <20%.

Cohort 2 (C2) population: will include all randomized patients in Cohort 2.

Pharmacokinetic population: will include a subset of approximately 20% of patients randomized to the A+ET arm who received at least 1 dose of abemaciclib and have at least 1 post-baseline evaluable PK sample

Statistical methods including methods for type 1-error control

The analysis of the primary endpoint, IDFS, to test the superiority of abemaciclib plus standard endocrine therapy to standard endocrine therapy will be performed on the ITT population and will use the log-rank test stratified by randomization factors.

Populations/endpoint that are type 1 error controlled

A sequential gate-keeping strategy was utilized to control the family-wise type I error at 0.025 (one-sided) for IDFS in:

- ITT,
- Ki-67 high (KI67H) and
- Cohort 1 Ki-67 high (C1-KI67H) populations.

That is, IDFS was tested hierarchically in the order of ITT, KI67H, then C1-KI67H populations, each gated after the former population. The cumulative one-sided alpha was controlled at 0.025 using a fixed alpha spending approach. The nominal one-sided alpha level at the two planned efficacy interim analyses was fixed at 0.003 for the first efficacy interim analysis and 0.010 for the second efficacy interim analysis. The remaining alpha will be spent at the final analysis.

In addition to the analysis described above, the Kaplan-Meier method will be used to estimate the IDFS curves as well as IDFS rates at every 12 months for each treatment group. Also, a stratified Cox proportional hazard model with treatment as a factor will be used to estimate the hazard ratio and corresponding 95% CI with Wald's test p-value after adjusting for the same randomization variable specified for the primary analysis. An additional unstratified Cox regression model will be employed to explore the effects of prognostic variables, such as the stratification variables and intrinsic/extrinsic factors.

Evaluating the efficacy, in terms of IDFS, for patients in KI67H and C1-KI67H populations was defined as secondary analyses.

The OS time was measured from the date of randomization to the date of death from any cause. For each patient who was not known to have died as of the data-inclusion cut-off date for a particular analysis, OS was censored at the date of last contact prior to the data inclusion cut-off date.

A sequential gate-keeping strategy was utilized to control the overall type I error at 0.025 (one-sided) for the secondary endpoint OS in all randomized patients in Cohort 1 and Cohort 2. That is, OS was tested only if IDFS in ITT, KI67H, C1-KI67H populations were all significant.

The final OS analysis is planned at 650 OS events or 10 years after last patient randomized, whichever occurred earlier.

The KM method was used to estimate the OS curve for each treatment arm. The OS rates for each arm were compared using a normal approximation for the difference between the rates, at the end of year 1 & 2, followed by yearly OS rates difference until approximately 200 patients in total were at risk. A stratified Cox proportional hazard model with treatment as a factor was used to estimate the HR between the 2 treatment arms and the corresponding CI and Wald p-value. Follow up time for OS was defined from the date of randomization and used the inverse of the censoring rules for OS. The median follow-up time was calculated using the KM method.

For health outcomes and quality of life assessments, for each instrument, percentage compliance was calculated as the number of completed assessments divided by the number of expected assessments (i.e., patients still on study). Percentage compliance was summarized by treatment groups at each assessment visit and overall. Reasons for noncompliance were summarized. A mixed effect, repeated measures model was applied to compare treatment arms by assessment with respect to each subscale and item score. The models included baseline score as a covariate and an unstructured covariance matrix was utilized. For each of the subscales and item scores, the analysis included all visits for which at least 25% of patients in each arm have an assessment. In the absence of published data on the minimally important difference of changes in the summary scores in the population of patients with EBC, an effect size of one-half standard deviation (0.5 SD) was used. This represents a conservative estimate of a minimally important difference (MID).

Missing data

Table 15. Rules for Determining Date of Event or Censor for Invasive Disease Free Survival

Situation	Date of Event or Censor	Event / Censor
IDFS event	Date of earliest IDFS event	Event
No IDFS event	Date of last assessment for recurrence	Censored
Unless		
No post-baseline disease recurrence assessment	Date of randomization	Censored
IDFS event documented after more than 12 months (+ 28 days)* following the last disease recurrence assessment or randomization (whichever is later)	Date of last assessment for recurrence prior to the documented IDFS event, or date of randomization (whichever is later)	Censored

*12 months (+28 days) is the longest allowed interval between visits in long-term follow up period after Year 5 defined by the schedule of activities

Abbreviation: IDFS = invasive disease-free survival.

Interim analysis

The futility analysis for IDFS will be conducted when approximately 130 events have been observed in ITT population. Futility should be declared if the observed IDFS hazard ratio is greater than 1.05. There are 2 planned efficacy interim analyses and 1 planned final analysis for IDFS in this study, which will be performed after approximately 195, 293, and 390 events have been observed in the ITT population. The cumulative 1-sided alpha will be controlled at 0.025, with an alpha split of 0.00000001 for the futility analysis and 0.02499999 for the planned efficacy analyses. If the analyses are

performed at exactly 195, 293, and 390 events, then the 1-sided boundary p-value at the final analysis will be 0.0220.

The design ensures control of the type 1-error for multiple interim analyses of the primary endpoint and the hypothesis testing of IDFS in multiple populations. OS can only be considered statistically significant once ITT, KI67H, C1-KI67H populations were all significant for IDFS. The plan was to perform interim 2 after 293 events, however there were a total of 323 IDFS events observed in the ITT population at the time of second efficacy interim analysis, including 136 patients in the A+ET arm and 187 patients in the ET only arm. This alters the significance level to be met for a positive efficacy conclusion. Based on the O'Brien-Fleming alpha spending function, this would require a two-sided p-value <0.0264 (p<0.0132, one-sided) according to the applicant.

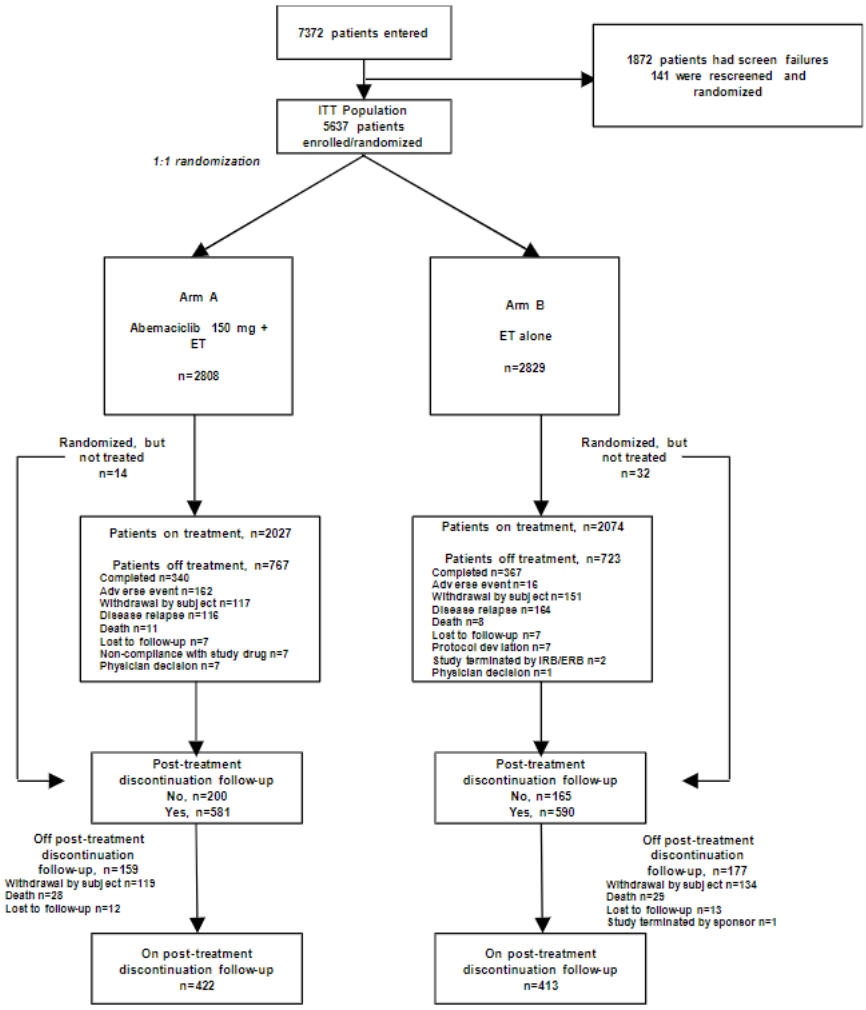
In addition, the alpha spending function was changed in amendment on 25 June 2019 from a fixed alpha level to using O'Brien-Fleming alpha spending. The timing (in terms of number of events) was altered accordingly.

Although the study protocol and the statistical methods documents stated that a one-sided test will be/was performed and that the interim analyses were planned accordingly, the results in the study report are presented as 2-sided p-values. It is assumed that the 2-sided p-values are derived from the 1-sided p-values.

The censoring rules to be applied for the time to event endpoints are presented but no other sensitivity or supplementary analyses to account for intercurrent events or missing data has been defined. This can be acceptable at this stage due to the need for updated results based on a longer follow-up.

Results

Participant flow



Recruitment

A total of 5637 patients from 38 countries were enrolled and randomized to one of the treatment arms in monarchE included in the ITT population. Patients randomized to the A+ET arm were treated with abemaciclib plus ET, and patients randomized to the ET only arm were treated with ET alone.

The first patient visit was 12 July 2017 and last patients first visit was 29 May 2019 for Cohort 1 and 12 August 2019 for Cohort 2.

Data cut-off dates:

Futility analysis: 08 July 2019

The first efficacy interim analysis: 27 September 2019

Second efficacy interim analysis for IDSF: 16 March 2020

Final IDFS analysis: 8 July 2020

First interim analysis OS: 1 April 2021 (included also updated analysis of IDFS/DFRS, this analysis was requested from FDA and not pre-planned)

Table 16. Efficacy Analysis timing

Analysis Point	Approximate Number of IDFS Events	Hazard Ratio for Futility	One-sided Boundary p-value for Efficacy	Cumulative Power Under H_1
Futility	130	1.05	N/A[a]	N/A
Interim 1	195	N/A	.0015 [b]	.222
Interim 2	293	0.95	.0092 [b]	.634
Final	390	N/A	.0220[b]	.861

OS analyses are planned to be performed at each of the analysis points specified in the above table, with the following 2 additional analyses:

- 2 years after the final IDFS analysis
- Final OS analysis: approximately 650 OS events or 10 years after last patient randomized, whichever occurs earlier

[a]An arbitrary alpha split of 0.00000001 is applied at the futility analysis.
[b]Dependent on the actual number of events observed at each analysis.

The number of patients enrolled and randomized per country summarized in descending order:

United States 820, Japan 377, China 357, Germany 300, Brazil 297, Spain 292, Republic of Korea 245, Turkey 235, Mexico 225, Australia 217, United Kingdom 199, France 187, Argentina 145, Russian Federation 139, Greece 138, Italy 131, Poland 125, Taiwan 124, Belgium 116, Romania 113, Denmark 112, India 112, Ukraine 105, Finland 94, Israel 77, Hungary 52, Canada 44, New Zealand 43, Austria 42, Portugal 37, Singapore 32, Czech Republic 27, Hong Kong 20, Netherlands 19, Saudi Arabia 14, Sweden 12, South Africa 9, Puerto Rico 4.

It was planned to enrol and randomise 4580 patients and to perform IA2 at 293 events, however the final number of randomised patients are 5637 and number of IDFS events at IA2 were 323. Over-randomisation was due to increased and variable recruitment, this should not be a major concern since the statistical methods allows for varying number of events at the time of the interim analysis while maintaining the type I error control.

Conduct of the study

Assessments of patients

During Years 1 and 2 (the on-study treatment period), patients will return to clinic every 2 weeks (15 ± 3 days) for the first 2 months, monthly (30 ± 5 days) starting with Month3 to Month 6, and every 3 months thereafter.

Long term follow-up (entered by all patients after completion of two year on-study treatment or after discontinuation of all study treatment after discontinuation criteria was met) continue up to year 10 with visits twice a year up to year 5 followed by once a year. After randomization, bilateral breast imaging was to be performed at yearly intervals (as recommended by international standard guidelines) or according to local standards. Abdominal and/or pelvic imaging (CT, PET/CT, MRI, or

ultrasound), chest imagine (PET/CT, CT or x-ray) and bone nuclear imaging (bone scan, PET, PET/CT) was to be performed locally only if clinically indicated per the investigator's judgement.

Protocol amendments

Table 17. MonarchE protocol amendments

Source: Table JPCF.3.1 p. 36 JPCF-04-Body.pdf

Trial Document	Approval Date
JPCF Protocol	10-March-2017
JPCF Protocol Amendment (a)	11-October-2017
JPCF Protocol Amendment (b)	29-June-2018
JPCF Protocol Amendment (c)	19-December-2018
JPCF Protocol Amendment (d)	25-June-2019
JPCF Protocol Amendment (e)	18-September-2019

Summary Amendment (a)

ET before randomization was changed from 8 weeks to 12 weeks and within 16 months (previously "within months/defined as 12 months") of definitive breast surgery for current malignancy.

Clarified primary objective specific for Cohort 1 and eligibility for Cohort 2 was defined as at least 1 positive node and Ki-67 status (details on testing added and clarified), not based on degree of axillary lymph node involvement, tumour size and histologic grade (as Cohort 1). Clarifications was made to the inclusion/exclusion criteria.

The schedule of activities and visits was modified and clarified. Data from MONARCH 1,2 and 3, including overall safety data and guidance including VTEs, ALT and AST increase was added. Toxicity dose adjustments and delays of abemaciclib was updated and hepatic safety monitoring was added.

Clarifications and additions for clarity were made.

Summary Amendment (b)

The number of patients screened, and number of patients planned to be included in monarchE was increased. Number of patients screened was increased by 1000, from 4200 to 5200 and number of patients included was increased from 3580 to 4580. The additional 1000 patient was intended for Cohort 1 where the number of patients was increased from 3080 to 4080.

The schedule of activities and also the inclusion criteria was modified and clarified. Text for safety monitoring of renal function, hepatic safety, VTE, for Ki-67 samples, determination of menopausal status was added and/or clarified.

Clarifications and additions for clarity were made.

Summary Amendment (c)

The primary objective ITT population was updated to include Cohort 2 (Cohort 2 eligibility was based solely on Ki-67 eligibility) as per regulatory recommendation from FDA. The number of events for the primary analysis of the primary endpoint IDFS was adjusted from 345 to 390. Also, the number of events for the interim analyses was updated. This also changed the secondary and exploratory populations for the IDFS endpoints, i.e. all Ki-67 high patients (regardless of cohort) was included in

the high analysis and the low and Ki-67 high from Cohort 2 was included as an exploratory analysis. The cap of 500 patients for Cohort 2 was removed.

Dose adjustment instructions for AST and VTE was added and additional instructions for dose adjustments for increased AST/ALT was added.

Clarifications and minor changes were also made.

Summary Amendment (d)

The major change was an update of the statistical plan with regards to the interim analysis, change of planned events and p-values. In addition, visit window for 3-monthly clinic visit and LTFU visits was extended, updates related to new AE information was introduced along with minor text revisions.

Summary Amendment (e)

Wording changed: "capsules" to "capsules or tablets" to support the updated supply chain switch to tablets.

Table 18. Timing of monarchE statistical analysis plan amendments

Trial Document	Approval Date
JPCF Statistical Analysis Plan	11-July-2017
JPCF Statistical Analysis Plan Version 2	06-December-2018
JPCF Statistical Analysis Plan Version 3	09-July-2019
JPCF Statistical Analysis Plan Version 4	11-December-2019
JPCF Statistical Analysis Plan Version 5	05-June-2020

Source: Table JPCF.3.3 p. 41 JPCF-04-Body.pdf

Table 19. Summary of Patients' Follow-Up Time and IDFS by Protocol Amendment Versions (Final IDFS Analysis).

	Cohort 1		Cohort 2	
	Abemaciclib+ET	ET alone	Abemaciclib+ET	ET alone

Initial protocol	**N = 262**	**N = 251**	**N = 9**	**N = 9**
Median follow-up, months	26.7	27.4	16.3	19.8
IDFS events, n (%)	15 (5.7)	25 (10.0)	2 (22.2)	0 (0.0)
Hazard ratio (95% CI)	Cohort 1 and Cohort 2: 0.684 (0.369, 1.266)			
Protocol Amendment (a)	**N = 1166**	**N = 1142**	**N = 74**	**N = 69**
Median follow-up, months	23.6	23.7	20.9	21.4
IDFS events, n (%)	89 (7.6)	113 (9.9)	6 (8.1)	2 (2.9)
Hazard ratio (95% CI)	Cohort 1 and Cohort 2: 0.821 (0.626, 1.077)			
Protocol Amendment (b)	**N = 754**	**N = 779**	**N = 96**	**N = 90**
Median follow-up, months	17.3	17.3	16.8	17.2
IDFS events, n (%)	33 (4.4)	58 (7.4)	3 (3.1)	6 (6.7)
Hazard ratio (95% CI)	Cohort 1 and Cohort 2: 0.577 (0.383, 0.868)			
Protocol Amendment (c)	**N = 373**	**N = 393**	**N = 74**	**N = 96**
Median follow-up, months	14.1	14.2	13.5	13.8
IDFS events, n (%)	15 (4.0)	27 (6.9)	0	1 (1.0)
Hazard ratio (95% CI)	Cohort 1 and Cohort 2: 0.587 (0.313, 1.099)			

Abbreviations: CI = confidence interval; ET = endocrine therapy; IDFS = invasive disease-free survival; ITT = intent-to-treat; N = number of patients in the ITT population; n = number of patients in specific population.
Note: All patients were enrolled to the study prior to when Protocol Amendments (d) and (e) were implemented.
Data cutoff: 08 July 2020
Source: t_tte_byamendment.rtf

Protocol deviations

Important protocol deviations occurred in 2.3% (64/2808) of patients treated with abemaciclib + ET and in 2.2% (61/2829) of patients treated with ET.

Several amendments and modifications were made to the study protocol, including changes related to the sample size, primary endpoint, statistical plan, interim analyses, including timing and number of events and inclusion/exclusion criteria. In addition, all amendments were done after inclusion of patients had started.

A sensitivity analysis based on the original SAP meets the predefined IDFS primary endpoint at the second interim analysis. The number of events for the final analysis of IDFS according to the original SAP had not been reached at the DCO of the second interim analysis. Thus, the study is considered positive at the second interim analysis which is reassuring in light of the changes performed to the SAP during the study. The final IDFS analysis, as defined in the initial SAP, was performed at the first OS interim analysis and did not deviate from the previous analysis.

The other changes e.g. related to update of formulation, Ki-67 tests, safety monitoring, dose adjustments due to AEs and clarifications is not considered to have compromised the integrity of the study or been driven by knowledge of study results.

There were no obvious differences between the treatment arms with regards important protocol deviations. The frequency is considered acceptable, and the protocol deviations is not likely to have affected with analyses or conclusions presented.

Baseline data

Table 20. Patient demographics, Cohort 1 population

Demographic Parameter[a]	Arm A Abemaciclib + ET N=2555	Arm B ET Alone N=2565	Total N=5120
Sex, n (%)	2555	2565	5120
Female	2535 (99.2)	2553 (99.5)	5088 (99.4)
Male	20 (0.8)	12 (0.5)	32 (0.6)
Age (years), n	2555	2565	5120
Mean (SD)	52.2 (11.3)	52.2 (11.2)	52.2 (11.3)
Median (min, max)	51.0 (23, 89)	51.0 (22, 86)	51.0 (22, 89)
Pooled age group, n (%)	2555	2565	5120
<65 years	2150 (84.1)	2190 (85.4)	4340 (84.8)
≥65 years	405 (15.9)	375 (14.6)	780 (15.2)
Race, n (%)	2522	2527	5049
American Indian or Alaska Native	55 (2.2)	55 (2.2)	110 (2.2)
Asian	622 (24.7)	605 (23.9)	1227 (24.3)
Black or African American	43 (1.7)	46 (1.8)	89 (1.8)
Native Hawaiian or Other Pacific Islander	3 (0.1)	4 (0.2)	7 (0.1)
White	1781 (70.6)	1794 (71.0)	3575 (70.8)
Multiple	18 (0.7)	23 (0.9)	41 (0.8)
Missing	33	38	71
Region, n (%)	2555	2565	5120
North America/Europe	1323 (51.8)	1330 (51.9)	2653 (51.8)
Asia	522 (20.4)	524 (20.4)	1046 (20.4)
Other	710 (27.8)	711 (27.7)	1421 (27.8)
Ethnicity, n (%)[b]	348	359	707
Hispanic or Latino	28 (8.0)	32 (8.9)	60 (8.5)
Not Hispanic or Latino	320 (92.0)	327 (91.1)	647 (91.5)
Missing	4	4	8
Menopausal status	2551	2565	5116
Premenopausal	1115 (43.7)	1105 (43.1)	2220 (43.4)
Postmenopausal	1436 (56.3)	1460 (56.9)	2896 (56.6)
Baseline ECOG PS	2554	2562	5116
0	2182 (85.4)	2147 (83.8)	4329 (84.6)
1	371 (14.5)	413 (16.1)	784 (15.3)
2	0	2 (0.1)	2 (<0.1)
3	1 (<0.1)	0	1 (<0.1)
Missing	1	3	4
Weight (kg), n	2532	2529	5061
Mean (SD)	71.3 (16.3)	71.7 (16.2)	71.5 (16.3)
Median (min, max)	68.7 (34.0, 165.2)	69.0 (35.3, 153.2)	68.9 (34.0, 165.2)
BMI (kg/m^2), n	2485	2507	4992
Mean (SD)	27.2 (5.9)	27.4 (5.8)	27.3 (5.9)
Median (min, max)	26.1 (15.6, 63.3)	26.4 (13.9, 65.3)	26.3 (13.9, 65.3)

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy; IDFS = invasive disease-free survival; ITT = intent to treat; max = maximum; min = minimum; N = number of patients in the ITT population; n = number of patients within a category; SD = standard deviation.

[a] Number of patients with non-missing data, used as a denominator.

[b] Only includes responses from the US sites, n is the number of subjects with a value of "HISPANIC OR LATINO" or "NOT HISPANIC OR LATINO."

Data cutoff: 08 July 2020.

Source: c_dm_summary_itt_cohort1.rtf

Source: monarchE Regulatory response_CHMP7(Cohrt1).

Table 21. Baseline disease characteristics - Cohort 1 population

	LY2835219-150mg +EDT (N=2555) n (%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
Pathological Diagnosis Term			
Invasive ductal breast carcinoma	1720 (67.3)	1762 (68.7)	3482 (68.0)
Breast cancer	421 (16.5)	420 (16.4)	841 (16.4)
Invasive lobular breast carcinoma	355 (13.9)	335 (13.1)	690 (13.5)
Mucinous breast carcinoma	27 (1.1)	11 (0.4)	38 (0.7)
Invasive papillary breast carcinoma	12 (0.5)	12 (0.5)	24 (0.5)
Inflammatory carcinoma of the breast	8 (0.3)	11 (0.4)	19 (0.4)
Medullary carcinoma of breast	7 (0.3)	6 (0.2)	13 (0.3)
Tubular breast carcinoma	3 (0.1)	5 (0.2)	8 (0.2)
Paget's disease of nipple	1 (0.0)	2 (0.1)	3 (0.1)
Metaplastic breast carcinoma	0 (0.0)	1 (0.0)	1 (0.0)
MISSING	1 (0.0)	0 (0.0)	1 (0.0)
Primary tumor size by radiology prior to any systemic treatment (Diameter in mm)			
n	2449	2461	4910
Mean (SD)	33.3 (22.6)	32.5 (20.6)	32.9 (21.6)
Median	27.0	27.0	27.0
Min - Max	0 - 200	0 - 130	0 - 200
<20 mm	695 (27.2)	673 (26.2)	1368 (26.7)
>=20 mm but <50 mm	1263 (49.4)	1325 (51.7)	2588 (50.5)
>=50 mm	491 (19.2)	463 (18.1)	954 (18.6)
MISSING	106 (4.1)	104 (4.1)	210 (4.1)
Primary tumor size by pathology following definitive surgery (Diameter in mm)			
n	2509	2540	5049
Mean (SD)	35.2 (27.0)	35.3 (25.0)	35.2 (26.0)
Median	28.0	28.0	28.0
Min - Max	0 - 550	0 - 190	0 - 550
<20 mm	676 (26.5)	656 (25.6)	1332 (26.0)
>=20 mm but <50 mm	1233 (48.3)	1278 (49.8)	2511 (49.0)
>=50 mm	600 (23.5)	606 (23.6)	1206 (23.6)
MISSING	46 (1.8)	25 (1.0)	71 (1.4)
Tumor Side			
LEFT	1322 (51.7)	1278 (49.8)	2600 (50.8)
RIGHT	1190 (46.6)	1260 (49.1)	2450 (47.9)
BILATERAL	42 (1.6)	27 (1.1)	69 (1.3)
MISSING	1 (0.0)	0 (0.0)	1 (0.0)
Involvement of Ipsilateral Supraclavicular, Ipsilateral Infraclavicular or Ipsilateral Internal Mammary Nodes at Initial Diagnosis			
YES	468 (18.3)	499 (19.5)	967 (18.9)
NO	2080 (81.4)	2060 (80.3)	4140 (80.9)
MISSING	7 (0.3)	6 (0.2)	13 (0.3)

	LY2835219-150mg +EDT (N=2555) n (%)	EDT (N=2565) n(%)	Total (N=5120) n(%)
Axillary lymph node evaluation - Results			
POSITIVE	2548 (99.7)	2559 (99.8)	5107 (99.7)
NEGATIVE	6 (0.2)	6 (0.2)	12 (0.2)
MISSING	1 (0.0)	0 (0.0)	1 (0.0)
Number of positive lymph nodes			
0	6 (0.2)	6 (0.2)	12 (0.2)
1	464 (18.2)	464 (18.1)	928 (18.1)
2	245 (9.6)	243 (9.5)	488 (9.5)
3	164 (6.4)	181 (7.1)	345 (6.7)
4	330 (12.9)	315 (12.3)	645 (12.6)
5	241 (9.4)	258 (10.1)	499 (9.7)
6	183 (7.2)	177 (6.9)	360 (7.0)
>=7	921 (36.0)	921 (35.9)	1842 (36.0)
MISSING	1 (0.0)	0 (0.0)	1 (0.0)
Number of positive lymph nodes - Category			
0	6 (0.2)	6 (0.2)	12 (0.2)
1-3	873 (34.2)	888 (34.6)	1761 (34.4)
4-9	1104 (43.2)	1119 (43.6)	2223 (43.4)
10 or more	571 (22.3)	552 (21.5)	1123 (21.9)
MISSING	1 (0.0)	0 (0.0)	1 (0.0)
Histopathological Grade at Initial Diagnosis			
G1 - LOW COMBINED HISTOLOGIC GRADE_FAVORABLE	186 (7.3)	190 (7.4)	376 (7.3)
G2 - INTERMEDIATE COMBINED HISTOLOGIC GRADE_MOD FAVORABLE	1181 (46.2)	1193 (46.5)	2374 (46.4)
G3 - HIGH COMBINED HISTOLOGIC GRADE_UNFAVORABLE	1063 (41.6)	1050 (40.9)	2113 (41.3)
GX - GRADE CANNOT BE ASSESSED	117 (4.6)	122 (4.8)	239 (4.7)
MISSING	8 (0.3)	10 (0.4)	18 (0.4)
Estrogen Receptor Measurement			
POSITIVE	2537 (99.3)	2548 (99.3)	5085 (99.3)
NEGATIVE	13 (0.5)	16 (0.6)	29 (0.6)
UNKNOWN	2 (0.1)	1 (0.0)	3 (0.1)
MISSING	3 (0.1)	0 (0.0)	3 (0.1)
Progesterone Receptor Measurement			
POSITIVE	2208 (86.4)	2226 (86.8)	4434 (86.6)
NEGATIVE	268 (10.5)	269 (10.5)	537 (10.5)
UNKNOWN	21 (0.8)	19 (0.7)	40 (0.8)
MISSING	58 (2.3)	51 (2.0)	109 (2.1)
Histopathological Diagnosis HER2 Status at Initial Diagnosis			
POSITIVE	0 (0.0)	2 (0.1)	2 (0.0)
NEGATIVE	2554 (100.0)	2563 (99.9)	5117 (99.9)
MISSING	1 (0.0)	0 (0.0)	1 (0.0)
Ki67 Results from Untreated Tumor - Central Lab (%)			
<20%	946 (37.0)	968 (37.7)	1914 (37.4)
>=20%	1017 (39.8)	986 (38.4)	2003 (39.1)
MISSING	463 (18.1)	471 (18.4)	934 (18.2)
Not Applicable	72 (2.8)	71 (2.8)	143 (2.8)
Not Evaluable	57 (2.2)	69 (2.7)	126 (2.5)
Tumor Stage			
Stage IA	1 (0.0)	0 (0.0)	1 (0.0)
Stage IIA	229 (9.0)	248 (9.7)	477 (9.3)
Stage IIB	281 (11.0)	286 (11.2)	567 (11.1)
Stage IIIA	1023 (40.0)	1018 (39.7)	2041 (39.9)
Stage IIIB	96 (3.8)	84 (3.3)	180 (3.5)
Stage IIIC	915 (35.8)	925 (36.1)	1840 (35.9)
MISSING	10 (0.4)	4 (0.2)	14 (0.3)

Source: Adapted from monarchE Regulatory response_CHMP7(Cohrt1).

Table 22. Prior medication and therapy, Cohort 1 population

	LY2835219-150mg+EDT (N=2555) n (%)	EDT (N=2565) n (%)	Total (N=5120) n (%)
Prior anti-cancer therapy			
Surgical procedure	2551 (99.8)	2565 (100.0)	5116 (99.9)
Radiotherapy	2452 (96.0)	2465 (96.1)	4917 (96.0)
Systemic therapy	2499 (97.8)	2513 (98.0)	5012 (97.9)
Surgical procedure: intent			
CURATIVE INTENT	2551 (99.8)	2565 (100.0)	5116 (99.9)
Radiotherapy: reason			
NEOADJUVANT	60 (2.3)	70 (2.7)	130 (2.5)
ADJUVANT	2401 (94.0)	2404 (93.7)	4805 (93.8)
Systemic therapy: reason and type			
NEO-ADJUVANT	960 (37.6)	968 (37.7)	1928 (37.7)
Chemo	932 (36.5)	930 (36.3)	1862 (36.4)
Endocrine	76 (3.0)	88 (3.4)	164 (3.2)
Other	6 (0.2)	5 (0.2)	11 (0.2)
Target	6 (0.2)	4 (0.2)	10 (0.2)
ADJUVANT	2223 (87.0)	2240 (87.3)	4463 (87.2)
Chemo	1597 (62.5)	1595 (62.2)	3192 (62.3)
Endocrine	1591 (62.3)	1611 (62.8)	3202 (62.5)
Other	2 (0.1)	2 (0.1)	4 (0.1)
Target	2 (0.1)	1 (0.0)	3 (0.1)
Term to be coded	1 (0.0)	0 (0.0)	1 (0.0)

Source: Adapted from monarchE Regulatory response_CHMP7(Cohrt1).

Table 23. Selected baseline disease characteristics by cohort

	COHORT 1 (N=5120) n (%)	COHORT 2 (N=517) n(%)
Number of positive lymph nodes		
0	12 (0.2)	2 (0.4)
1	931 (18.2)	256 (49.5)
2	490 (9.6)	162 (31.3)
3	344 (6.7)	79 (15.3)
4	644 (12.6)	7 (1.4)
5	498 (9.7)	1 (0.2)
6	360 (7.0)	3 (0.6)
>=7	1839 (35.9)	7 (1.4)
MISSING	2 (0.0)	0 (0.0)
Number of positive lymph nodes - Category		
0	12 (0.2)	2 (0.4)
1-3	1765 (34.5)	497 (96.1)
4-9	2219 (43.3)	11 (2.1)
10 or more	1122 (21.9)	7 (1.4)
MISSING	2 (0.0)	0 (0.0)
Histopathological Grade at Initial Diagnosis		
G1 - LOW COMBINED HISTOLOGIC GRADE_FAVORABLE	376 (7.3)	48 (9.3)
G2 - INTERMEDIATE COMBINED HISTOLOGIC GRADE_MOD FAVORABLE	2374 (46.4)	394 (76.2)
G3 - HIGH COMBINED HISTOLOGIC GRADE_UNFAVORABLE	2113 (41.3)	43 (8.3)
GX - GRADE CANNOT BE ASSESSED	239 (4.7)	27 (5.2)
MISSING	18 (0.4)	5 (1.0)
Tumor Stage		
Stage IA	1 (0.0)	2 (0.4)
Stage IIA	477 (9.3)	199 (38.5)
Stage IIB	567 (11.1)	209 (40.4)
Stage IIIA	2035 (39.7)	16 (3.1)
Stage IIIB	186 (3.6)	9 (1.7)
Stage IIIC	1839 (35.9)	73 (14.1)
MISSING	15 (0.3)	9 (1.7)

Source: Modified from Table JPCF.8.6. p. 233-237 JPCF-04-body.pdf

Numbers analysed

Table 24. Analysis populations.

Analysis Population[a] n (%)	Arm A Abemaciclib + ET	Arm B ET	Total
ITT	2808	2829	5637
Safety	2794	2797	5591
Ki67H (C1 + C2)	1262	1233	2495
Ki67L (C1 + C2)	953	973	1926
C1	2555	2565	5120
C1-Ki67H	1017	984	2001
C1-Ki67L	946	967	1913
C2	253	264	517
Pharmacokinetic	486	NA	486

Abbreviations: C1 = Cohort 1; C2 = Cohort 2; ET = endocrine therapy; ITT = intent-to-treat; KI67H = Ki-67 High; KI67L = Ki-67 Low; NA = not assessed; RT = randomized and treated.
[a]IDFS and DRFS were assessed in the Ki67H, Ki67L, C1-Ki67H, C1-Ki67L, and C2 groups.
Scource: Table JPCF.4.4. p. 48 jpcf-04-body.pdf

Table 25. Duration of drug exposure categories

	Arm A Abemaciclib + ET N=2791		Arm B ET N=2800	
Number (%) of patients	At start of study	Any time	At start of study	Any time
Aromatase inhibitors	1928 (69.1)	2018 (72.3)	1891 (67.5)	2005 (71.6)
Anastrozole	611 (21.9)	661 (23.7)	617 (22.0)	705 (25.2)
Exemestane	225 (8.1)	286 (10.2)	228 (8.1)	330 (11.8)
Letrozole	1092 (39.1)	1166 (41.8)	1046 (37.4)	1140 (40.7)
Anti-estrogens	863 (30.9)	891 (31.9)	909 (32.5)	969 (34.6)
Tamoxifen	857 (30.7)	883 (31.6)	898 (32.1)	959 (34.3)
Toremifene	6 (0.2)	10 (0.4)	11 (0.4)	11 (0.4)
GnRH Analogues	NA	606 (21.7)	NA	627 (22.4)
Goserelin	NA	422 (15.1)	NA	450 (16.1)
Leuprorelin	NA	236 (8.5)	NA	210 (7.5)
Triptorelin	NA	28 (1.0)	NA	37 (1.3)

Abbreviations: ET = endocrine therapy; GnRH = gonadotropin-releasing hormones; N = number of patients in the safety population; NA = not applicable.

Source: Table JPCF.4.12. p. 62 JFCF-04-body.pdf.

In Cohort 1 at the first IA for OS, 73.3% of the patients had completed 2 years on study treatment and 17.4% of patients had discontinued early from the study treatment period. 0.8% of patients were never treated. 8.5% of patients are still on study treatment.

Table 26. Summary of Patient Disposition - Cohort 1 population (DCO 1 April 2021, IA1 OS)

n (%)	Arm A Abemaciclib + ET N=2555	Arm B ET Alone N=2565	Total N=5120
Never treated	13 (0.5)	29 (1.1)	42 (0.8)
Treated	2542 (99.5)	2536 (98.9)	5078 (99.2)
On treatment	215 (8.4)	218 (8.5)	433 (8.5)
Off treatment	2327 (91.1)	2318 (90.4)	4645 (90.7)
Completed treatment period	1872 (73.3)	1883 (73.4)	3755 (73.3)
Discontinued early	455 (17.8)	435 (17.0)	890 (17.4)

Abbreviations: ET = endocrine therapy; N = number of patients in the Cohort 1 population; n = number of patients in the specific population.

Data cutoff: 01 April 2021.

Source: monarchE Regulatory response_CHMP7(Cohrt1).

Use of GnRH analogues in relation to menopausal status and use of bisphosphonates

A total of 43.4% of patients in Cohort 1 were premenopausal and about 23% of patients received GnRH analogues. The menopausal status was reported at the time of the diagnosis and the choice of GnRH analogues was made at the start of adjuvant ET treatment. Menopausal status at the time when adjuvant ET was started was not recorded.

Table 27. Summary of First Endocrine Therapy on Study by Menopausal Status - Cohort 1 safety population (DCO 1 April 2021, IA1 OS)

	Premenopausal		Postmenopausal	
	Abemaciclib + ET	ET Alone	Abemaciclib + ET	ET Alone
	N=1111	N=1091	N=1425	N=1448
Aromatase inhibitors as the first ET	465 (41.9)	441 (40.4)	1284 (90.1)	1288 (89.0)
With GnRH analogues	354 (31.9)	326 (29.9)	21 (1.5)	34 (2.3)
Without GnRH analogues	111 (10.0)	115 (10.5)	1263 (88.6)	1254 (86.6)
Tamoxifen as the first ET	640 (57.6)	644 (59.0)	141 (9.9)	161 (11.1)
With GnRH analogues	194 (17.5)	215 (19.7)	5 (0.4)	6 (0.4)
Without GnRH analogues	446 (40.1)	429 (39.3)	136 (9.5)	155 (10.7)

Abbreviations: ET = endocrine therapy; GnRH = gonadotropin-releasing hormone; IA = interim analysis; ITT = intent to treat; N = number of patients in the ITT population; OS = overall survival.

Data cutoff: 01 April 2021.

Source: monarchE Regulatory response_CHMP7(Cohrt1).

In Cohort 1 aromatase inhibitors was administered to 68.9% in the A+ET arm and 68.1% in the ET only arm at study start and anti-oestrogens were administered to 31.1% in the A+ET arm and 31.9% in the ET only arm. Subgroup results for the different classes of ET have been provided (Table 40)Table 40.

In Cohort 1, bisphosphonate agents were administered at the discretion of the investigators and were used by 14.3% of patients in the abemaciclib plus ET arm and 16.8% of patients in the ET only arm.

Table 28. Bone-Modifying Agents, - Cohort 1 safety population (DCO 1 April 2021, IA1 OS)

Agent, n (%)	The A+ET Arm Abemaciclib + ET N=2539	The ET Alone Arm ET N=2539
General concomitant medications	2414 (95.1)	2205 (86.8)
Bisphosphonate agents[a]	364 (14.3)	427 (16.8)
Zoledronic acid	279 (11.0)	317 (12.5)
Alendronic acid	45 (1.8)	60 (2.4)
Ibandronic acid	31 (1.2)	35 (1.4)
Risedronic acid	13 (0.5)	25 (1.0)
Clodronic acid	3 (0.1)	1 (<0.1)
Minodronic acid	2 (0.1)	0
Alendronic acid; colecalciferol	1 (<0.1)	2 (0.1)
Colecalciferol, risedronic acid	0	1 (<0.1)
Pamidronic acid	0	1 (<0.1)

Abbreviations: A = abemaciclib; ET = endocrine therapy; ITT = intent to treat; N = number of patients in the ITT population; n = number of patients within a category.

[a] Patients who received more than 1 bisphosphonate drug are only counted once under the total number of bisphosphonate agent use.

Data cutoff: 01 April 2021.

Source: monarchE Regulatory response_CHMP7(Cohrt1).

A total of 43.4% of patients were premenopausal, whereas about 23% of patients received GnRH analogues. The frequency of patients with AI and TAM +/- GnRH analogues for pre- and postmenopausal women respectively was balanced across treatment arms. GnRH analogues was more commonly used among the younger patients in the study as is expected.

Outcomes and estimation

Data from three data different cut-offs are presented.

The second interim analysis (DCO 16 March 2020) – median follow-up time approximately 15.5 months (ITT population).

The final IDFS analysis (DCO July 2020) - median follow-up time approximately 19 months (ITT population).

The OS first interim analysis (DCO 1 April 2021) - median follow-up time 27.7 months and median follow-up time for patients off treatment 6.0 months (Cohort 1 population).

IDFS in the ITT-population (DCO 16 March 2020)

A total of 323 IDFS events were observed in the ITT population at the time of second efficacy interim analysis, including 136 patients in the A+ET arm and 187 patients in the ET only arm. Based on the O'Brien-Fleming alpha spending function, this would require a two-sided p-value <0.0264 in order to claim a positive efficacy at this interim analysis. By the interim analysis cut-off date, the median follow- up time was 15.4 months in the A+ET arm and 15.5 months in the ET only arm.

The primary endpoint of IDFS was met for this study at the second efficacy interim analysis, demonstrating a statistically significant improvement (two-sided p=.0096) in IDFS with the A+ET arm compared to the ET only arm, HR=0.747, 95% CI: 0.598, 0.932). A summary of IDFS in ITT population is shown in *Table 29*.

Table 29. Summary of investigator-assessed IDFS - ITT population (DCO 16 March 2020, IA2)

	Arm A Abemaciclib + ET N=2808	Arm B ET N=2829	Treatment Effect/Difference 2 sided p-Value[f]
Number of events, n (%)	136 (4.8)	187 (6.6)	
Deaths without invasive disease	13 (0.5)	6 (0.2)	
Invasive disease	123 (4.4)	181 (6.4)	
Number of patients censored, n (%)	2672 (95.2)	2642 (93.4)	
Invasive disease prior to randomization	2 (0.1)	2 (0.1)	
No post-baseline assessment	23 (0.8)	45 (1.6)	
No documented invasive disease	2647 (94.3)	2595 (91.7)	
Minimum, months[a]	0.03+	0.03	
25th percentile (95% CI)	-	- (25.7, -)	
Median (95% CI) months	-	-	
75% percentile (95% CI)	-	-	
Maximum, months[a]	30.7+	30.9+	
Restricted mean (95% CI) with restriction time = 25.2 months[b]	24.2 (24.1, 24.4)	23.9 (23.7, 24.1)	0.3 (0.1, 0.6), p=.0112[e]
p-value (2-sided) log-rank	Stratified[c]: p=.00957 Unstratified: p=.00815		
HR (95% CI)	Stratified[c]: 0.747 (0.598, 0.932) Unstratified: 0.743 (0.596, 0.927)		
IDFS rate, % (95% CI)[d]			
12 months	96.5 (95.7, 97.1)	95.7 (94.9, 96.4)	0.7 (-0.3, 1.8), p=.1628
24 months	92.2 (90.4, 93.7)	88.7 (86.5, 90.5)	3.5 (0.9, 6.1), p=.0073

[a]For minimum and maximum, + indicates a censored observation. [b]Restriction time is defined by the latest time where the standard error of the survival estimates are ≤0.075.[c]Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status.[d]95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.[e]2-sided p-value based on normal approximation. [f]Treatment Effect/Difference/p-values are computed based on comparator ET

Source: Table JPCF.5.1. p. 66 JPCF-04-body.pdf

Updated IDFS (OS first interim analysis) – ITT population

A total of 565 IDFS events were observed in the ITT population at the final IDFS analysis (DCO 1 April 2021), including 232 (8.3%) patients in the A+ET arm and 333 (11.8%) patients in the ET only arm. The median duration of follow-up was 27.1 versus 27.2 months in the A+ET arm and the ET only arm, respectively. The HR estimate was 0.696 (95% CI: 0.588, 0.823). A summary of IDFS and DRFS in ITT population is shown in Table 30. K-M curves of IDFS in ITT population are displayed in Figure 5.

Table 30. Summary of IDFS in the ITT Population (DCO 1 April 2021, IA1 OS)

	Abemaciclib plus ET N=2808	**ET alone N=2829**
Invasive Disease-Free Survival (IDFS)		
Number of patients with event, n (%)	232 (8.3)	333 (11.8)
Log rank p-value (2-sided)	Stratified[a]: p=.00002 Unstratified: p=.00002	
Hazard ratio (95% CI)	Stratified[a]: 0.696 (0.588, 0.823) Unstratified: 0.697 (0.589, 0.82)	
IDFS rates at 2 years (%, 95% CI)	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)
IDFS rates at 3 years (%, 95% CI)	88.8 (87.0, 90.3)	83.4 (81.3, 85.3)

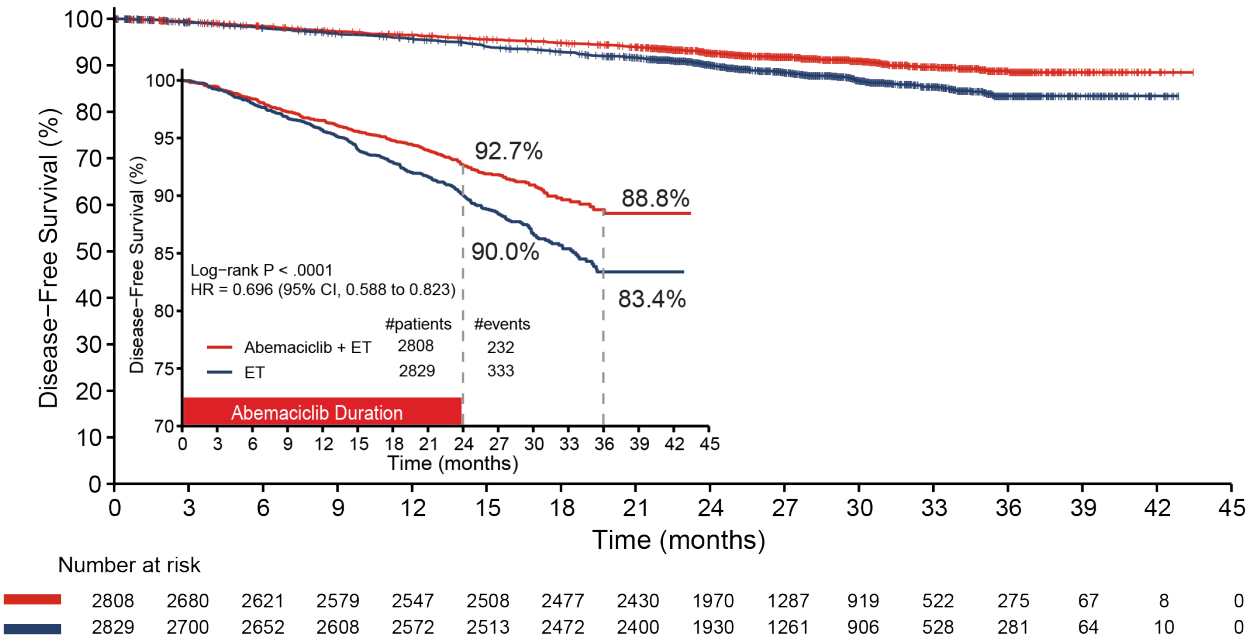
Abbreviations: CI = confidence interval; ET = endocrine therapy; ITT = intent-to-treat; IWRS= interactive web-response system; n = number of patients in specific population; N = number of patients in the ITT population.

[a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status.

Data cutoff: 01 April 2021.

Sources: o_tte_summ_idfs_itt; o_tte_summ_drfs_itt/ monarchE CHMP Second Request Supplementary Information

Figure 4. Kaplan-Meier plot of IDFS by investigator assessment at OS Interim Analysis 1 – ITT Population



Abbreviations: # = number of; CI = confidence interval; DRFS = distant relapse-free survival; ET = endocrine therapy; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival.

Note: p-Value is nominal. Data cutoff: 01 April 2021.

Sources: km_idfs_itt_v1.pdf; km_idfs_itt_v2.pdf; o_tte_summ_idfs_itt.rtf/ monarchE CHMP Second Request Supplementary Information

Ancillary analyses

IDFS in Ki-67 High Population

Among the 2495 randomized patients with Ki-67 ≥20% (Ki67H population) in both Cohort 1 and Cohort 2, a statistically significant IDFS was observed for patients with high Ki-67 index (≥20%) in the ITT population (2-sided p-value boundary at 0.0424) at the final IDFS analysis. 82 events were observed in the A+ET arm and 115 events in the ET only arm (HR 0.691 (95% CI 0.519, 0.920, p=0.0072)). IDFS results for Ki67H patients from the first OS interim analysis are presented in Table 32.

IDFS in Cohort 1 Ki-67 High Population

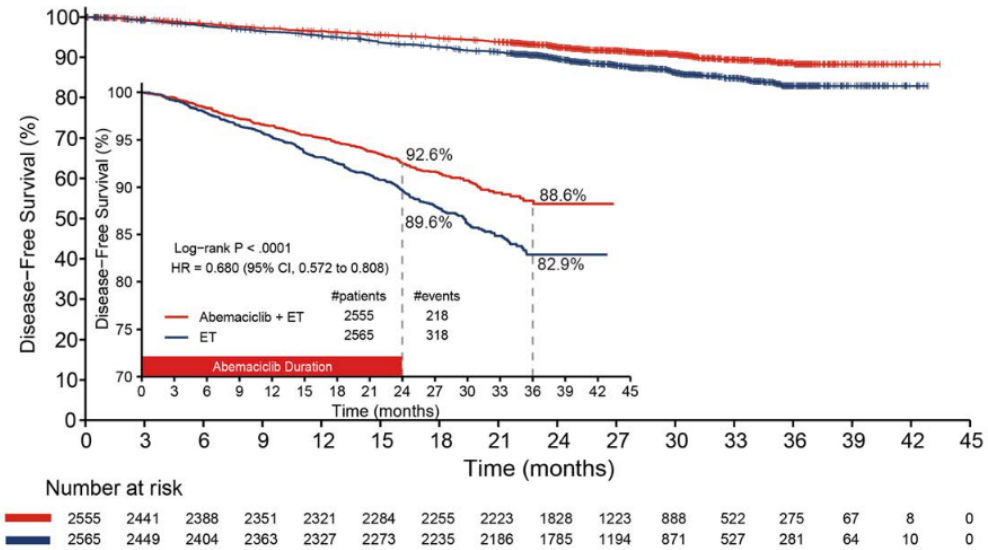
Among the 2001 randomized patients with Ki-67 ≥20% in Cohort 1 (C1-Ki67H population), a statistically significant treatment effect in IDFS was observed for patients in C1-Ki67H population (2-sided p-value boundary at 0.0426) at the final IDFS analysis. 71 events as observed in the A+ET arm and 106 events in the ET only arm (HR 0.643 (95% CI 0.475, 0.872, p=0.0040)). IDFS results for patients with C1-Ki67H from the first OS interim analysis are presented in Table 32.

IDFS in Cohort 1 Population

Analyses of Cohort 1 was not specified in the final protocol. 5120 patients were randomized with clinicopathological features: ≥4pALN or 1-3 pALN and at least one of the following two criteria: tumour size ≥5 cm or; histological grade 3.

In the updated results for IDFS in the Cohort 1 population 536 IDFS events were observed, with 218 (8.5%) events in the A+ET arm and 318 (12.4%) events in the ET only arm at the first OS interim analysis. The HR estimate was 0.680 (95% CI 0.572, 0.808) between the A+ET arm and the ET only arm, for patients in the Cohort 1 population. IDFS results for patients in Cohort 1 from the first OS interim analysis are presented in Table 31 and K-M curves are displayed in Figure 6.

Figure 5. Kaplan-Meier plot of IDFS by investigator assessment – Cohort 1 population (DCO 1 April 2021, IA1 OS)



Note: p-value is nominal.
Abbreviations: # = number of; CI = confidence interval; ET = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival.
Data cutoff: 01 April 2021.
Source: km_idfs_cohort1_v1.pdf; km_idfs_cohort1_v2.pdf; o_tte_summ_idfs_3_cohort1.rtf.

Source: JPCF 04 Body, Figure JPCF.8.1. p. 192/1871

Table 31. Summary of investigator-assessed IDFS – Cohort 1 population (DCO 1 April 2021, IA1 OS)

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*d
Number of Events, n (%)	218 (8.5)	318 (12.4)	
Death without Invasive Disease, n (%)	15 (0.6)	10 (0.4)	
Invasive Disease, n (%)	203 (7.9)	308 (12.0)	
Number of Patients Censored, n (%)	2337 (91.5)	2247 (87.6)	
Invasive Disease prior to randomization, n (%)	2 (0.1)	2 (0.1)	
No Post-Baseline Assessment, n (%)	22 (0.9)	41 (1.6)	
No documented ID with regular assessment, n (%)	2313 (90.5)	2204 (85.9)	
Minimum *a, month	0.03+	0.03	
25th percentile (95% CI)	- (- , -)	- (- , -)	
Median (95% CI)	- (- , -)	- (- , -)	-
75th percentile (95% CI)	- (- , -)	- (- , -)	
Maximum	43.46+	42.87+	
p-value (2-sided) - Log Rank Unstratified			p = 0.00001
- Log Rank Stratified*b			p = 0.00001
Hazard Ratio (95% CI) - UnStratified			0.682(0.574, 0.811)
- Stratified*b			0.680(0.572, 0.808)
Invasive Disease-Free Survival Time 1 Survival Rate (%) with 95% CI *c			
12 - month	96.5 (95.7, 97.2)	95.3 (94.4, 96.1)	1.2 (0.1, 2.3) p = 0.0360
24 - month	92.6 (91.4, 93.5)	89.6 (88.3, 90.8)	3.0 (1.3, 4.6) p = 0.0003
36 - month	88.6 (86.7, 90.1)	82.9 (80.7, 84.8)	5.7 (3.0, 8.4) p = <.0001

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable.
Note: Quartiles and Invasive Disease-Free Survival Time 1 Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*a - For minimum and maximum, + indicates a censored observation;
*b - Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status
*c - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*d - Treatment Effect/Difference/p-values are computed based on comparator EDT
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Data Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr3/data/analysis/shared/adam

Source: JPCF 04 Body, Table JPCF.8.9. p. 190-191/1871

IDFS in complementary populations

IDFS results for complementary patient populations are presented in Table 32 along with the primary analysis populations for comparison.

Table 32. Summary of investigator-assessed IDFS by cohort and Ki-67 status – (DCO 1 April 2021, IA1 OS)

IDFS, n (%)	Abemaciclib+ET (events (% of pts)	ET (events (% of pts)	Stratified HR (95% CI)
ITT	232 (8.3)	333 (11.8)	0.696 (0.588, 0.823)
Ki67 High ITT	118 (9.4)	172 (13.9)	0.663 (0.524, 0.839)
Cohort 1 Ki67 High	104 (10.2)	158 (16.0)	0.626 (0.488, 0.803)
Cohort 1 Ki67 Low	62 (6.6)	86 (8.9)	0.704 (0.506, 0.979)
Cohort 1 Ki67 missing*	52 (8.8)	611 (12.1)	0.705 (0.495, 1.005)*
Cohort 1	218 (8.5)	318 (12.4)	0.680 (0.572, 0.808)
Cohort 2	14 (5.5)	15 (5.7)	0.986 (0.475, 2.048)

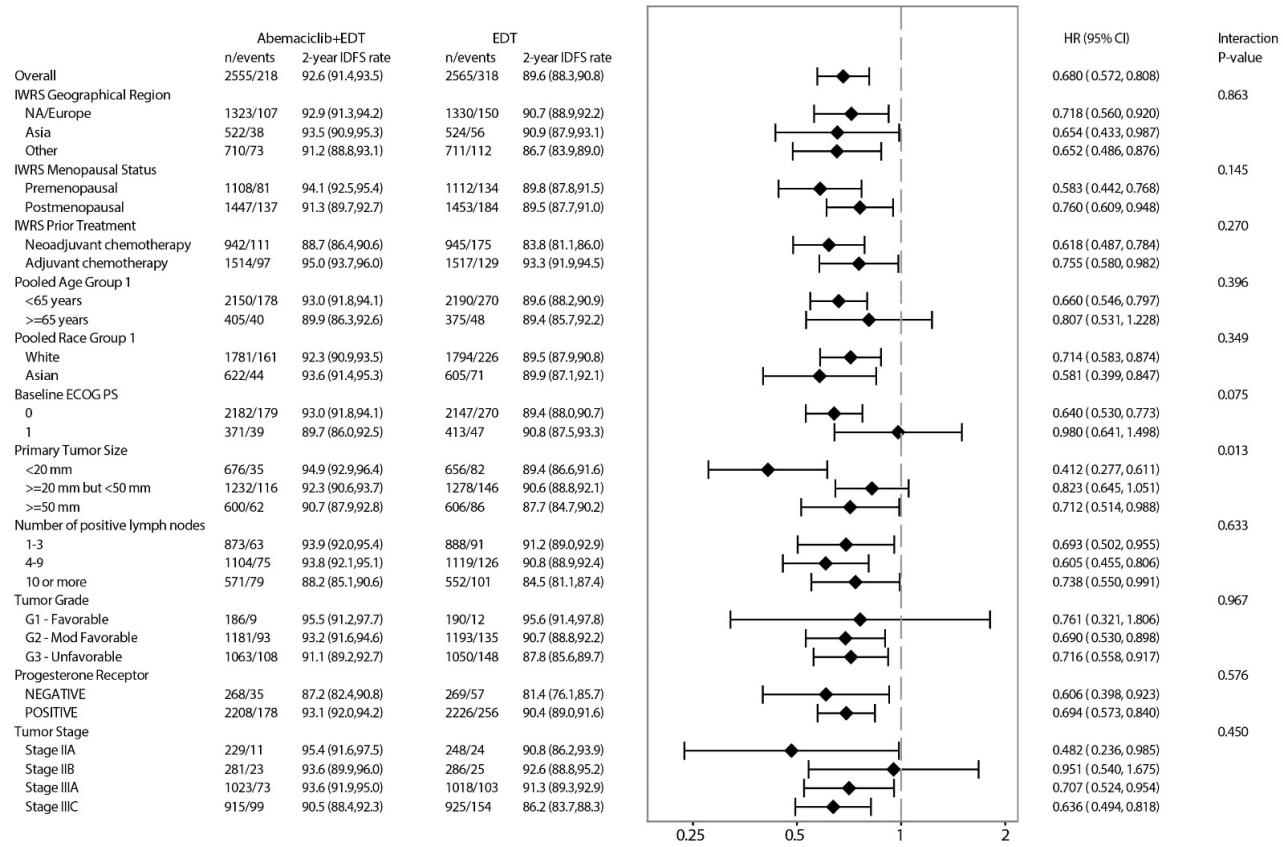
*presented HR is unstratified, events derived from the interaction analysis o
Ki67 index, JPCF.5.13. p. 59/1871

Source: Adapted from JPCF 04 Body, Tables JPCF.5.9-13.

IDFS subgroup analysis of Cohort 1

Subgroup analyses for the Cohort 1 population based on IA1 OS are presented in Figure 7.

Figure 6. Subgroup forest plot of IDFS – Cohort1 population (DCO 1 April 2021, IA1 OS)



Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EDT = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; IWRS = interactive web-response system; n = number of patients in the specific population; NA = North America. Data cutoff: 01 April 2021.
Source: monarchE Regulatory response_CHMP7(Cohrt1).

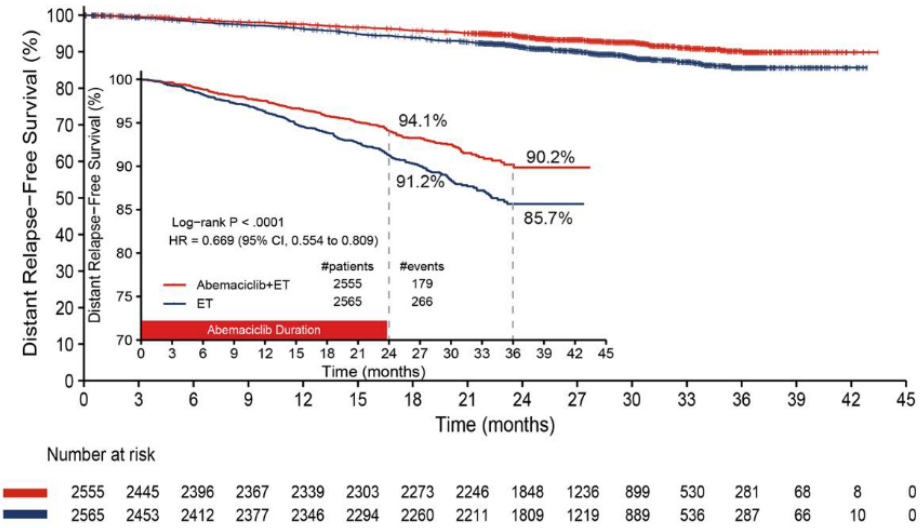
Distant Relapse-Free Survival – DRFS

In Cohort 1 at the IA1 OS analysis was 179 (7.0%) and 266 (10.4%) events recorded in the A+ET arm and the ET only arm respectively. The HR estimate was 0.669 (95% CI 0.554, 0.809). Results are presented in Figure 8 and Table 33.

Subgroup results based on Ki-67 and cohort are presented in Table 34.

DRFS subgroup results from IA1 OS for the Cohort 1 population are presented in Figure 9.

Figure 7. Kaplan-Meier plot of DRFS by investigator assessment – Cohort 1 population (DCO 1 April 2021, IA1 OS)



Note: p-value is nominal.
Abbreviations: # = number of; CI = confidence interval; DRFS = distant relapse-free survival; ET = endocrine therapy; HR = hazard ratio; OS = overall survival.
Data cutoff: 01 April 2021.
Sources: km_drfs_cohort1_v1.pdf; km_drfs_cohort1_v2.pdf; o_tte_summ_drfs_3_cohort1.rtf.

Source: JPCF 04 Body, Figure JPCF8.5. p. 204/1871

Table 33. Summary of investigator-assessed DRFS – Cohort 1 population (DCO 1 April 2021, IA1 OS)

	LY2835219-150mg+EDT (N=2555)	EDT (N=2565)	Treatment Effect/Difference / p-value*d
Number of Events, n (%)	179 (7.0)	266 (10.4)	
Death without Distant Relapse, n (%)	19 (0.7)	16 (0.6)	
Distant Relapse, n (%)	160 (6.3)	250 (9.7)	
Number of Patients Censored, n (%)	2376 (93.0)	2299 (89.6)	
Distant Relapse prior to randomization, n (%)	2 (0.1)	2 (0.1)	
No Post-Baseline Assessment, n (%)	22 (0.9)	41 (1.6)	
No documented DR with regular assessment, n (%)	2352 (92.1)	2256 (88.0)	
Minimum *a, month	0.03+	0.03	
25th percentile (95% CI)	- (- , -)	- (- , -)	
Median (95% CI)	- (- , -)	- (- , -)	-
75th percentile (95% CI)	- (- , -)	- (- , -)	
Maximum	43.46+	42.87+	
p-value (2-sided) - Log Rank Unstratified			p = 0.00003
- Log Rank Stratified*b			p = 0.00003
Hazard Ratio (95% CI) - UnStratified			0.671(0.555, 0.810)
- Stratified*b			0.669(0.554, 0.809)
Distant Relapse-Free Survival Time Survival Rate (%) with 95% CI *c			
12 - month	97.5 (96.8, 98.1)	96.3 (95.5, 97.0)	1.2 (0.3, 2.2) p = 0.0124
24 - month	94.1 (93.0, 95.0)	91.2 (90.0, 92.3)	2.8 (1.4, 4.3) p = 0.0002
36 - month	90.2 (88.4, 91.7)	85.7 (83.6, 87.5)	4.5 (2.0, 7.0) p = 0.0004

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable.
Note: Quartiles and Distant Relapse-Free Survival Time Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*a - For minimum and maximum, + indicates a censored observation;
*b - Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status
*c - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*d - Treatment Effect/Difference/p-values are computed based on comparator EDT
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Data Location: /lillyce/prd/ly2835219/i3y_mc_jpcf/csr3/data/analysis/shared/adam

Source: JPCF 04 Body, Table JPCF.8.13.. p. 202-203/1871

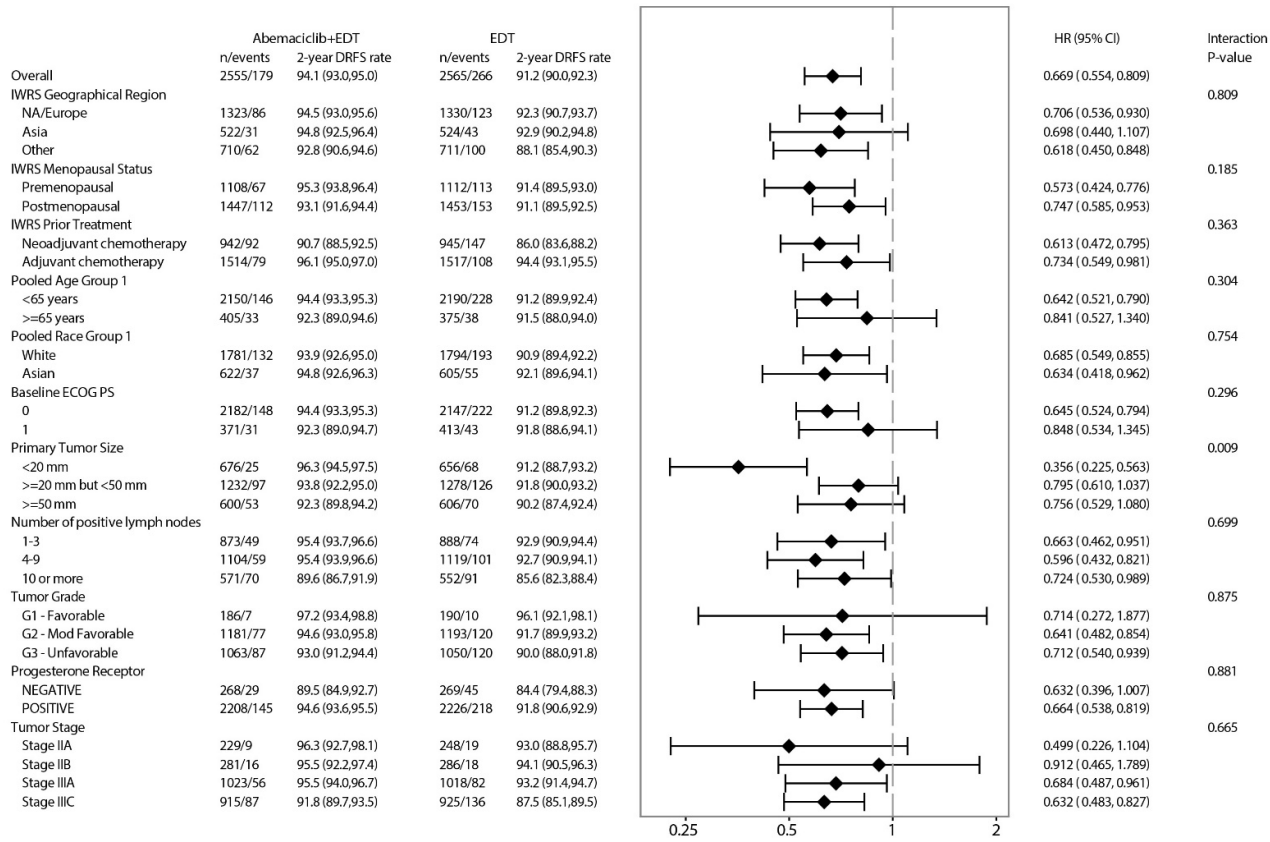
Table 34. Summary of secondary and exploratory analyses for DRFS by cohort and Ki-67 status –(DCO 1 April 2021, IA1 OS)

DRFS	Abemaciclib+ET (events (% of pts)	ET (events (% of pts)	Stratified HR (95% CI)
Ki67 High ITT	97 (7.7)	146 (11.8)	0.639 (0.494, 0.827)
Cohort 1 Ki67 High	85 (8.4)	135 (13.7)	0.599 (0.456, 0.787)
Cohort 1 Ki67 Low	50 (5.3)	73 (7.5)	0.679 (0.473, 0.975)
Cohort 1 Ki67 missing*	44 (7.4)	58 (9.5)	0.766* (0.518, 1.134)
Cohort 1	179 (7.0)	266 (10.4)	0.669 (0.554, 0.809)
Cohort 2	12 (4.7)	12 (4.5)	1.040 (0.467, 2.318)

**presented HR is unstratified, events derived from the interaction analysis of Ki67 index, JPCF.5.13. p. 59/1871*

Source: Adapted from JPCF 04 Body, Tables JPCF.5.9-13.

Figure 8. Subgroup forest plot of DRFS – Cohort 1 population (DCO 1 April 2021, IA1 OS)



Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EDT = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; IWRS = interactive web-response system; n = number of patients in the specific population; NA = North America. Data cutoff: 01 April 2021.

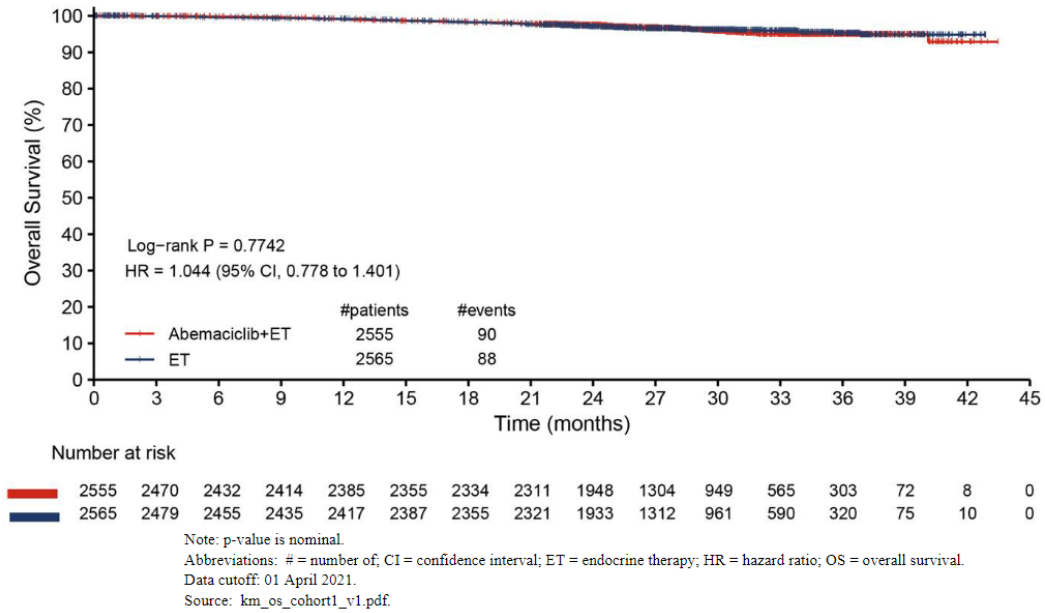
Source: monarchE Regulatory response_CHMP7(Cohrt1).

Overall Survival – OS

In Cohort 1 at IA1 OS there were 90 deaths (3.5%) in the A+ET arm, and 88 deaths (3.4%) in the ET only arm. The HR estimate for OS was 1.044 (95% CI 0.778, 1.401). For K-M curves of the Cohort 1 population of OS at IA1 OS refer to Figure 10.

The subgroup analysis of OS based on Ki-67 is presented in Table 35. The majority of deaths in both arms are due to study disease (Table 36).

Figure 9. Kaplan-Meier plot of OS – Cohort 1 population first OS interim analysis (DCO 1 April 2021)



Note: p-value is nominal.
Abbreviations: # = number of; CI = confidence interval; ET = endocrine therapy; HR = hazard ratio; OS = overall survival.
Data cutoff: 01 April 2021.
Source: km_os_cohort1_v1.pdf.

Source: JPCF 04 Body, Figure JPCF8.9. p. 218/1871

Table 35. Summary of subgroup analysis of OS by cohort and Ki-67 status – (DCO 1 April 2021, IA1 OS)

OS,	Abemaciclib+ET (events (% of pts)	ET (events (% of pts)	Stratified HR (95% CI)
Ki67 High ITT	48 (3.8)	55 (4.4)	0.851 (0.577, 1.255)
Cohort 1 Ki67 High	42 (4.1)	53 (5.4)	0.767 (0.511, 1.152)
Cohort 1 Ki67 Low*	27 (2.9)	20 (2.1)	1.402* (0.786, 2.500)
Cohort 1 Ki67 missing*	21 (3.5)	15 (2.5)	1.424* (0.734, 2.763)
Cohort 1	90 (3.5)	88 (3.4)	1.044 (0.778, 1.401)
Cohort 2	6 (2.4)	2 (0.8)	Immature

*presented HR is unstratified, events derived from the interaction analysis of Ki67 index, JPCF.5.13. p. 59/1871
Source: Adapted from JPCF 04 Body, Tables JPCF.5.9-13.

Table 36. Deaths and reasons of deaths by subpopulation - ITT population OS interim analysis (DCO 1 April 2021)

	Arm A Abemaciclib + ET N=2808	Arm B ET Alone N=2829
C1-Ki67 High, N	**1017**	**986**
Deaths, n	42	53
Prior to Treatment, n	0	0
Due to Study Disease, n	36	45
Due to Adverse Event, n	6	8
C1-Ki67 Low, N	**946**	**968**
Deaths, n	27	20
Prior to Treatment, n	0	0
Due to Study Disease, n	15	16
Due to Adverse Event, n	12	4
C1-Ki67 missing, N	**592**	**611**
Deaths, n	21	15
Prior to Treatment[a], n	1[a]	1[a]
Due to Study Disease, n	17	12
Due to Adverse Event, n	3	2
Cohort 2, N	**253**	**264**
Deaths, n	6	2
Prior to Treatment, n	0	0
Due to Study Disease, n	3	2
Due to Adverse Event, n	3	0

Abbreviations: C1-Ki67 High = Cohort 1 with Ki-67 high; C1-Ki67 Low = Cohort 1 with Ki-67 low; ET – endocrine therapy; ITT = intent-to-treat; N = number of patients in the ITT population; n = number of patients in the specific population; OS = overall survival.

a Deaths after randomization and prior to treatment were due to study disease.

Data cutoff: 01 April 2021.

Sources: o_ds_death_by_reason_5_cohort1_ki67_high.rtf; o_ds_death_by_reason_5_cohort1_ki67_low.rtf; o_ds_death_by_reason_5_cohort1.rtf; o_ds_death_by_reason_5_cohort2.rtf; t_tte_ki67subgrp_os.rtf

Source: JPCF 04 Body Table JPCF.5.14. p. 60/1871.

Sensitivity analysis according to original SAP (version 1)– DCO 8 July 2020 and DCO 1 April 2021

SAP Version 1 was the initial version and aligned with the initial study protocol. The primary analysis population was Cohort 1. This document was approved prior to first patient visit.

Table 37. Summary of Prespecified Analyses Details Under Initial SAP Version (Sensitivity Analyses) and Current SAP

	Initial SAP (Sensitivity Analyses) Planned N = 3080 (**Cohort 1**)		**Current SAP (Version 5)** Planned N = 4580 (**Cohorts 1 and 2**)	
	Target number of IDFS events	2-sided p-value boundary [a]	Target number of IDFS events	2-sided p-value boundary [b]
Interim 1	115	0.010	195	0.003
Interim 2	230	0.010	293	0.0184
Final IDFS	345	0.0408	390	0.0440

Abbreviations: IDFS = invasive disease-free survival; N = number of patients in the ITT population; SAP = statistical analysis plan.

[a] Using fixed alpha at interim 1 and 2, and p-value boundary at final IDFS analysis is dependent on the actual number of events observed at each analysis.

[b] Using O'Brien-Fleming alpha spending function, dependent on the actual number of events observed at each analysis.

Source: SAP Version 1 (Appendix 2); SAP Version 5 (Appendix 6)

Table 38. IDFS in the ITT Population (Cohort 1) Under Initial SAP Version at Each of the Locked Databases

Data Cutoff	**Analysis Time Point under Current SAP**	**Initial SAP (Sensitivity Analyses), N=3081, Cohort 1**			
		Number of IDFS events	**Analysis Time Point**	**IDFS Hazard Ratio (95% CI) Stratified p-Value**	**Outcome**
16 March 2020	IA2	224	IA2 (required 230 events)	0.692 (0.529, 0.904) 2-sided p=.0067	Statistically significant at IA2 (p<.01)
08 July 2020	Final IDFS Analysis	268	Not Specified Analysis Time Point	0.702 (0.550, 0.896) 2-sided p=.0043	Not a prespecified analysis
01 April 2021	OS IA1	370	Final IDFS (required 345 events)	0.669 (0.544, 0.824) 2-sided p=.0001	

Abbreviations: CI = confidence interval; IA1 = Interim Analysis 1; IA2 = Interim Analysis 2; IDFS = invasive disease-free survival; ITT = intent-to-treat; N = number of patients in the ITT population; SAP = statistical analysis plan.

Sources: o_tte_summ_idfs_randcut.rtf (IA2 data)
:o_tte_summ_idfs_randcut.rtf (Final IDFS Analysis data)
: o_tte_summ_idfs_3_cohort1_sensitivity.rtf (OS IA1 data)

Table 39. Summary of IDFS and DRFS in the ITT Population (Cohort 1) under Initial SAP Version using IA2 Database and Cutoff Date (16 March 2020)

Cohort 1	**Abemaciclib plus ET N = 1538**	**ET alone N = 1543**
Invasive Disease-Free Survival (IDFS)		
Number of patients with event, n (%)	90 (5.9)	134 (8.7)
Log-rank p-value, 2-sided	Stratified[a]: p = 0.00673 Unstratified: p = 0.00591	
Hazard ratio (95% CI)	Stratified[a]: 0.692 (0.529, 0.904) Unstratified: 0.689 (0.527, 0.900)	
IDFS rates at 2 years (%, 95% CI)	92.3 (90.3, 93.8)	88.6 (86.3, 90.5)
Distant Relapse-Free Survival (DRFS)		
Number of patients with an event, n (%)	74 (4.8)	110 (7.1)
Log-rank p-value, 2-sided	Stratified[a]: p = 0.01477 Unstratified: p = 0.01381	
Hazard ratio (95% CI)	Stratified[a]: 0.693 (0.516, 0.932) Unstratified: 0.692 (0.515, 0.929)	
DRFS rates at 2 years (%, 95% CI)	93.5 (91.7, 95.0)	90.3 (88.2, 92.1)

Abbreviations: CI = confidence interval; DRFS = distant relapse-free survival; ET = endocrine therapy; IA2 = interim analysis 2; IDFS = invasive disease-free survival; ITT = intent-to-treat; ITT = intent-to-treat; N = number of patients in the ITT population SAP = statistical analysis plan.

[a] Stratified by IWRS Geographical Region, IWRS Prior Treatment, IWRS Menopausal Status.

Source: o_tte_summ_idfs_randcut.rtf; o_tte_summ_drfs_randcut.rtf

IDFS and DRFS Analyses by ET-subgroup in Cohort 1

Table 40. IDFS and DRFS Analyses in Different Classes of ET Subgroups Cohort 1 population (DCO 1 April 2021, IA1 OS)

	First ET=Tamoxifen		First ET=Aromatase Inhibitors	
	Abemaciclib + ET (N=783)	**ET Alone (N=805)**	**Abemaciclib + ET (N=1753)**	**ET Alone (N=1725)**
Number of IDFS events, n	59	110	158	206
IDFS hazard ratio (95% CI)	0.537 (0.392, 0.737)		0.760 (0.618, 0.935)	
2-year IDFS rates, % (95% CI)	94.1 (92.1, 95.5)	89.2 (86.8, 91.2)	91.9 (90.5, 93.1)	89.9 (88.3, 91.2)
Number of DRFS events, n	50	93	129	171
DRFS hazard ratio (95% CI)	0.539 (0.383, 0.761)		0.748 (0.595, 0.940)	
2-year DRFS rates, % (95% CI)	95.0 (93.2, 96.4)	91.0 (88.7, 92.8)	93.6 (92.3, 94.7)	91.4 (90.0, 92.7)

Abbreviations: CI = confidence interval; DRFS = distant relapse-free survival; ET = endocrine therapy; IDFS = invasive disease-free survival; N = number of patients in the ITT population; n = number of patients in the specific population; ITT = intent to treat.

Note: Twenty-one patients in the abemaciclib + ET arm and 43 patients in the ET alone arm were not treated or received toremifene as the first ET. Among them, 1 vs 2 IDFS events and 0 vs 1 DRFS events were observed per treatment arm. Data cutoff: 01 April 2021

Source: monarchE Regulatory response_CHMP7(Cohrt1).

Frequency of IDFS and DRFS events and HR favours abemaciclib addition regardless of backbone ET. 95% CI for IDFS and DRFS rate at 2 years per treatment arm is overlapping as well as 95% CI for HR per treatment arm for each backbone ET for IDFS and DRFS.

Tumour Recurrence Locations in Cohort 1

Table 41. Tumour recurrence locations – first occurrence - Cohort 1 population (DCO 1 April 2021, IA1 OS)

Location of Recurrence	LY2835219-150mg +EDT (N=2555)	EDT (N=2565)	Total (N=5120)
Patients with Any Disease Recurrence	203 (7.9)	308 (12.0)	511 (10.0)
Local/Regional Recurrence	33 (1.3)	50 (1.9)	83 (1.6)
Distant Recurrence	146 (5.7)	233 (9.1)	379 (7.4)
Contralateral Recurrence	8 (0.3)	12 (0.5)	20 (0.4)
Second Primary Neoplasm	19 (0.7)	20 (0.8)	39 (0.8)
Patients with Local Recurrence			
BREAST	9 (0.4)	12 (0.5)	21 (0.4)
CHEST WALL	4 (0.2)	9 (0.4)	13 (0.3)
SKIN OF BREAST	0 (0.0)	5 (0.2)	5 (0.1)
SKIN OF CHEST WALL	6 (0.2)	3 (0.1)	9 (0.2)
Patients with Regional Recurrence			
AXILLA	1 (0.0)	4 (0.2)	5 (0.1)
AXILLARY LYMPH NODE	8 (0.3)	7 (0.3)	15 (0.3)
INFRACLAVICULAR LYMPH NODE	1 (0.0)	2 (0.1)	3 (0.1)
INTERNAL MAMMARY LYMPH NODE	0 (0.0)	1 (0.0)	1 (0.0)
SUPRACLAVICULAR LYMPH NODE	7 (0.3)	7 (0.3)	14 (0.3)
Patients with Distant Recurrence			
BONE	62 (2.4)	119 (4.6)	181 (3.5)
BRAIN	7 (0.3)	20 (0.8)	27 (0.5)
CENTRAL NERVOUS SYSTEM	6 (0.2)	2 (0.1)	8 (0.2)
LIVER	42 (1.6)	65 (2.5)	107 (2.1)
LUNG	31 (1.2)	35 (1.4)	66 (1.3)
LYMPH NODE	10 (0.4)	14 (0.5)	24 (0.5)
PERITONEUM	0 (0.0)	2 (0.1)	2 (0.0)
PLEURA	1 (0.0)	13 (0.5)	14 (0.3)
SKIN	1 (0.0)	2 (0.1)	3 (0.1)
SOFT TISSUE	1 (0.0)	2 (0.1)	3 (0.1)
OTHER	15 (0.6)	14 (0.5)	29 (0.6)
Patients with Contralateral Recurrence			
BREAST	6 (0.2)	7 (0.3)	13 (0.3)
LYMPH NODE	2 (0.1)	5 (0.2)	7 (0.1)
Patients with Second Primary Neoplasm			
BONE MARROW	2 (0.1)	1 (0.0)	3 (0.1)
COLON	1 (0.0)	2 (0.1)	3 (0.1)
ENDOMETRIUM	0 (0.0)	1 (0.0)	1 (0.0)
LUNG	2 (0.1)	3 (0.1)	5 (0.1)
LYMPHATIC SYSTEM	1 (0.0)	1 (0.0)	2 (0.0)
OVARY	0 (0.0)	2 (0.1)	2 (0.0)
STOMACH	1 (0.0)	0 (0.0)	1 (0.0)
OTHER	12 (0.5)	10 (0.4)	22 (0.4)

Source: Adapted from monarchE Regulatory response_CHMP7(Cohrt1).

Post-Discontinuation Therapies in Cohort 1

At the time of the first OS interim analysis, 8.5% of the patients were still on study treatment in Cohort 1. Among patients treated with abemaciclib +ET 80.7% had received post discontinuation systemic therapy and 80.5% from the ET arm in Cohort 1. The most common post-discontinuation systemic therapy received was ET. The proportion of patients reported to received chemotherapy after discontinuing study treatment was 3.3% in the abemaciclib +ET and 4.0% in the ET the A+ET arm in Cohort 1 at the first interim analysis for OS.

Table 42. Post-discontinuation therapies for cancer – Cohort 1 population (DCO 1 April 2021, IA1 OS)

Parameter	LY2835219-150mg+EDT (N=2555) n(%)		EDT (N=2565) n(%)		Total (N=5120) n(%)	
Surgical procedure	30	(1.2)	48	(1.9)	78	(1.5)
Radiotherapy	39	(1.5)	62	(2.4)	101	(2.0)
Systemic therapy						
Overall	2061	(80.7)	2065	(80.5)	4126	(80.6)
Chemo	85	(3.3)	102	(4.0)	187	(3.7)
AZACITIDINE	1	(0.0)	0	(0.0)	1	(0.0)
CAPECITABINE	33	(1.3)	44	(1.7)	77	(1.5)
CARBOPLATIN	16	(0.6)	16	(0.6)	32	(0.6)
CARBOPLATIN;PACLITAXEL	1	(0.0)	0	(0.0)	1	(0.0)
CISPLATIN	7	(0.3)	9	(0.4)	16	(0.3)
CYCLOPHOSPHAMIDE	10	(0.4)	6	(0.2)	16	(0.3)
DECITABINE	0	(0.0)	1	(0.0)	1	(0.0)
DOCETAXEL	8	(0.3)	13	(0.5)	21	(0.4)
DOXORUBICIN	6	(0.2)	5	(0.2)	11	(0.2)
EPIRUBICIN	2	(0.1)	3	(0.1)	5	(0.1)
ERIBULIN	14	(0.5)	5	(0.2)	19	(0.4)
FLUOROURACIL	1	(0.0)	4	(0.2)	5	(0.1)
GEMCITABINE	16	(0.6)	20	(0.8)	36	(0.7)
GIMERACIL;OTERACIL;TEGAFUR	1	(0.0)	3	(0.1)	4	(0.1)
METHOTREXATE	3	(0.1)	2	(0.1)	5	(0.1)
MITOMYCIN	2	(0.1)	0	(0.0)	2	(0.0)
MITOXANTRONE	2	(0.1)	0	(0.0)	2	(0.0)
NEDAPLATIN	0	(0.0)	1	(0.0)	1	(0.0)
OXALIPLATIN	0	(0.0)	1	(0.0)	1	(0.0)
PACLITAXEL	29	(1.1)	27	(1.1)	56	(1.1)
SACITUZUMAB GOVITECAN	1	(0.0)	0	(0.0)	1	(0.0)
TEMOZOLOMIDE	0	(0.0)	2	(0.1)	2	(0.0)
TESETAXEL	0	(0.0)	1	(0.0)	1	(0.0)
VINCRISTINE	1	(0.0)	0	(0.0)	1	(0.0)
VINORELBINE	3	(0.1)	9	(0.4)	12	(0.2)
Endocrine	2008	(78.6)	2005	(78.2)	4013	(78.4)
AMCENESTRANT	0	(0.0)	1	(0.0)	1	(0.0)
ANASTROZOLE	455	(17.8)	431	(16.8)	886	(17.3)
EXEMESTANE	205	(8.0)	239	(9.3)	444	(8.7)
FULVESTRANT	36	(1.4)	83	(3.2)	119	(2.3)
GOSERELIN	192	(7.5)	205	(8.0)	397	(7.8)
LETROZOLE	792	(31.0)	769	(30.0)	1561	(30.5)
LEUPRORELIN	110	(4.3)	114	(4.4)	224	(4.4)
TAMOXIFEN	559	(21.9)	552	(21.5)	1111	(21.7)
TOREMIFENE	7	(0.3)	3	(0.1)	10	(0.2)
TRIPTORELIN	22	(0.9)	24	(0.9)	46	(0.9)
Other	12	(0.5)	9	(0.4)	21	(0.4)
ATEZOLIZUMAB	3	(0.1)	2	(0.1)	5	(0.1)
DENDRITIC CELLS CYTOKINE INDUCED KILLER CELLS	1	(0.0)	0	(0.0)	1	(0.0)
DENOSUMAB	1	(0.0)	0	(0.0)	1	(0.0)
ETHANOL	1	(0.0)	0	(0.0)	1	(0.0)
IMMUNOTHERAPY	1	(0.0)	1	(0.0)	2	(0.0)
IODINE (131 I)	0	(0.0)	1	(0.0)	1	(0.0)
PEMBROLIZUMAB	1	(0.0)	2	(0.1)	3	(0.1)
PERTUZUMAB	5	(0.2)	3	(0.1)	8	(0.2)
RITUXIMAB	1	(0.0)	0	(0.0)	1	(0.0)
ZOLEDRONIC ACID	1	(0.0)	0	(0.0)	1	(0.0)
Target	40	(1.6)	125	(4.9)	165	(3.2)
ABEMACICLIB	1	(0.0)	31	(1.2)	32	(0.6)
ALPELISIB	2	(0.1)	1	(0.0)	3	(0.1)
BEVACIZUMAB	8	(0.3)	10	(0.4)	18	(0.4)
CHIDAMIDE	1	(0.0)	0	(0.0)	1	(0.0)
EVEROLIMUS	1	(0.0)	4	(0.2)	5	(0.1)
NERATINIB	1	(0.0)	0	(0.0)	1	(0.0)
OLAPARIB	1	(0.0)	2	(0.1)	3	(0.1)
PALBOCICLIB	15	(0.6)	58	(2.3)	73	(1.4)
PROTEIN KINASE INHIBITORS	0	(0.0)	1	(0.0)	1	(0.0)
RIBOCICLIB	5	(0.2)	23	(0.9)	28	(0.5)
TALAZOPARIB	1	(0.0)	2	(0.1)	3	(0.1)
TRASTUZUMAB	8	(0.3)	4	(0.2)	12	(0.2)
TRASTUZUMAB EMTANSINE	2	(0.1)	0	(0.0)	2	(0.0)
XENTUZUMAB	0	(0.0)	1	(0.0)	1	(0.0)

Source: Adapted from monarchE Regulatory response_CHMP7(Cohrt1).

There are no major differences between the treatment arms with regard to post discontinuation therapies.

Health Outcomes and Quality-of Life Evaluation in Cohort 1

After the baseline assessment, FACT-B, FACT-ES, 2 FACIT-sourced items of cognitive symptoms, 3 FACIT-sourced items for bladder symptoms, FACIT-F and EQ-5D-5L questionnaires were next administered to patients at visit 6, visit 9, visit 15, and visit 21 (approximate timepoints of visits, 3, 6, 12 and 18 months respectively). Questionnaires were given at visit 27 (end of on study treatment period) and follow-up visits are not included in IA2 due to <25% of patients having an assessment at those visits.

Table 43. FACT-B - Cohort 1 safety population (DCO 8 July 2020, Final IDFS).

	Arm A Abemaciclib + ET N=2555			Arm B ET N=2565		Arm A vs Arm B	
	N	Mean (SD)	Change from Baseline, LS Mean (SE)	N	Mean (SD)	Change from Baseline, LS Mean (SE)	LS Mean Change Difference (SE)
FACT-B Total Score							
Baseline	2165	108.16 (18.03)	NA	2184	107.05 (18.06)	NA	NA
Visit 6 (3 months)	2100	106.56 (19.04)	-1.53 (0.27)	2108	107.54 (18.58)	0.38 (0.27)	-1.91 (0.38)
Visit 9 (6 months)	2045	107.16 (19.56)	-1.08 (0.29)	2058	107.96 (18.52)	0.70 (0.29)	-1.78 (0.41)
Visit 15 (12 months)	1947	106.88 (19.58)	-1.53 (0.32)	1939	108.09 (18.81)	0.83 (0.32)	-2.36 (0.45)
Visit 21 (18 months)	1300	106.05 (19.75)	-2.03 (0.37)	1298	108.77 (18.46)	1.25 (0.37)	-3.28 (0.52)
All post-baseline	NE	NE	-1.54 (0.25)	NE	NE	0.79 (0.25)	-2.33 (0.35)

Abbreviations: ET = endocrine therapy; FACT-B = Functional Assessment of Cancer Therapy – Breast; IDFS = invasive disease-free survival; LS Mean = least-squares mean; N = number of patients in the safety population; NA = not applicable; NE = not evaluated; SD = standard deviation; SE = standard error.
Data cutoff: 08 July 2020.

Source: monarchE Regulatory response_CHMP7(Cohrt1).

Table 44. FACT-ES - Cohort 1 safety population (DCO 8 July 2020, Final IDFS)

	Arm A Abemaciclib + ET N=2555			Arm B ET N=2565			Arm A vs Arm B
	N	Mean (SD)	Change from Baseline, LS Mean (SE)	N	Mean (SD)	Change from Baseline, LS Mean (SE)	LS Mean Change Difference (SE)
ESS-19							
Baseline	2173	62.24 (9.07)	NA	2188	61.43 (9.49)	NA	NA
Visit 6 (3 months)	2113	59.49 (10.28)	-2.68 (0.15)	2116	60.57 (9.80)	-1.02 (0.15)	-1.66 (0.21)
Visit 9 (6 months)	2054	59.65 (10.61)	-2.69 (0.16)	2072	60.17 (10.13)	-1.44 (0.16)	-1.25 (0.23)

	Arm A Abemaciclib + ET N=2555			Arm B ET N=2565			Arm A vs Arm B
	N	Mean (SD)	Change from Baseline, LS Mean (SE)	N	Mean (SD)	Change from Baseline, LS Mean (SE)	LS Mean Change Difference (SE)
ESS-19							
Visit 15 (12 months)	1957	59.27 (10.86)	-3.06 (0.18)	1949	59.94 (10.35)	-1.74 (0.18)	-1.32 (0.25)
Visit 21 (18 months)	1308	59.01 (10.85)	-3.34 (0.21)	1302	60.17 (10.29)	-1.75 (0.21)	-1.59 (0.29)
All post-baseline	NE	NE	-2.94 (0.14)	NE	NE	-1.49 (0.14)	-1.45 (0.20)
ESS-23							
Baseline	2128	75.33 (10.62)	NA	2145	74.25 (11.23)	NA	NA
Visit 6 (3 months)	2040	71.79 (12.06)	-3.49 (0.17)	2054	73.30 (11.69)	-1.20 (0.17)	-2.29 (0.25)
Visit 9 (6 months)	1984	72.13 (12.48)	-3.35 (0.19)	2007	72.97 (12.00)	-1.57 (0.19)	-1.78 (0.27)
Visit 15 (12 months)	1884	71.86 (12.69)	-3.66 (0.21)	1890	72.77 (12.22)	-1.85 (0.21)	-1.81 (0.29)
Visit 21 (18 months)	1265	71.51 (12.78)	-4.06 (0.24)	1260	73.05 (12.23)	-1.75 (0.24)	-2.30 (0.35)
All post-baseline	NE	NE	-3.64 (0.17)	NE	NE	-1.59 (0.16)	-2.05 (0.23)

Abbreviations: ET = endocrine therapy; FACT-ES = Functional Assessment of Cancer Therapy – Endocrine Subscale; IDFS = invasive disease-free survival; LS Mean = least-squares mean; N = number of patients in the safety population; NA = not applicable; NE = not evaluated; SD = standard deviation; SE = standard error.
Data cutoff: 08 July 2020.
Source: monarchE Regulatory response_CHMP7(Cohrt1).

Table 45. EQ-5D-5L Index and VAS Score i - Cohort 1 safety population (DCO 8 July 2020, Final IDFS

	Arm A Abemaciclib + ET N=2555			Arm B ET Alone N=2565			Arm A vs Arm B
	N	Mean (SD)	Change from Baseline, LS Mean (SE)	N	Mean (SD)	Change from Baseline, LS Mean (SE)	LS Mean Change Difference (SE)
EQ-5D-5L Health State Index (UK)							
Baseline	2136	0.79 (0.17)	NA	2141	0.78 (0.17)	NA	NA
Visit 6 (3 months)	2051	0.78 (0.17)	-0.01 (0.00)	2041	0.77 (0.18)	-0.01 (0.00)	0.00 (0.00)
Visit 9 (6 months)	1986	0.78 (0.18)	-0.01 (0.00)	2003	0.78 (0.18)	-0.01 (0.00)	0.00 (0.00)
Visit 15 (12 months)	1901	0.78 (0.18)	-0.01 (0.00)	1886	0.78 (0.18)	-0.01 (0.00)	0.00 (0.00)
Visit 21 (18	127	0.77	-0.02 (0.00)	125	0.78	-0.01 (0.00)	-0.01 (0.00)

	Arm A Abemaciclib + ET N=2555			Arm B ET Alone N=2565			Arm A vs Arm B
	N	Mean (SD)	Change from Baseline, LS Mean (SE)	N	Mean (SD)	Change from Baseline, LS Mean (SE)	LS Mean Change Difference (SE)
months)	8	(0.19)		5	(0.19)		
All post-baseline	NE	NE	-0.01 (0.00)	NE	NE	-0.01 (0.00)	0.00 (0.00)
EQ-5D-5L Visual Analogue Scale Score							
Baseline	2138	78.03 (15.91)	NA	2146	78.07 (15.40)	NA	NA
Visit 6 (3 months)	2041	77.13 (16.12)	-1.06 (0.27)	2052	79.19 (15.27)	0.95 (0.27)	-2.01 (0.39)
Visit 9 (6 months)	1995	78.56 (15.51)	0.16 (0.28)	2019	80.25 (15.13)	1.89 (0.28)	-1.73 (0.39)
Visit 15 (12 months)	1903	79.25 (15.64)	0.66 (0.29)	1881	80.46 (14.97)	2.00 (0.29)	-1.34 (0.41)
Visit 21 (18 months)	1266	79.14 (15.28)	0.39 (0.34)	1265	80.94 (15.39)	2.04 (0.34)	-1.65 (0.48)
All post-baseline	NE	NE	0.04 (0.23)	NE	NE	1.72 (0.23)	-1.68 (0.32)

Abbreviations: ET = endocrine therapy; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; IDFS = invasive disease-free survival; LS Mean = least-squares mean; N = number of patients in the safety population; NA = not applicable; NE = not evaluated; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

Data cutoff: 08 July 2020.

Source: monarchE Regulatory response_CHMP7(Cohrt1).

The timing of the assessments did not allow to capture the effects of any AEs the patient might have experienced during the first 3 months is considered a limitation and reduced quality of life for patients experiencing AEs early in the course of treatment have not been recorded.

The mean scores and changes from baseline scores appear similar in both arms for FACT-B, EACT-ES, EQ-5D-5L index and VAS scores.

Summary of main study(ies)

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

Table 46. Summary of Efficacy for monarchE

Title: monarchE		
Study identifier	monarchE, I3Y-MC-JPCF	
Design	A Phase 3, global, randomized, open label study of abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, HR+, HER2-, breast cancer	
	Duration of main phase:	FPI: July 2017 LPI: August 2019
Hypothesis	Superiority	

Treatments groups	Abemaciclib +ET		150 mg abemaciclib twice daily + Standard adjuvant ET of physician's choice. Abemaciclib treatment was given for up to 2 years. ET was given for 5 years or 10 if medically indicated.
	ET		Standard adjuvant ET of physician's choice. ET was given for 5 years or 10 if medically indicated.
Endpoints and definitions	Primary endpoint	IDFS	Invasive disease-free survival time is measured from the date of randomization to the date of first occurrence of: • Ipsilateral invasive breast tumour recurrence • regional invasive breast cancer recurrence • distant recurrence • death attributable to any cause • contralateral invasive breast cancer • second primary non-breast invasive cancer Recurrence of non-invasive breast cancer was not counted as an event.
	Secondary endpoint	IDFS for patients with pre-treatment Ki-67 index ≥20% by central lab	See above.
	Secondary endpoint	DRFS	Distance relapse free survival (DRFS) was measured from the date of randomization to the date of first occurrence of: • Distant recurrence • Death attributable to any cause
Database lock	16 March 2020, second interim analysis 8 July 2020, final IDFS analysis 1 April 2021, first OS interim analysis		

Results and Analysis

Analysis description	**Interim Analysis**			
Analysis population and time point description	Intent to treat, second interim analysis			
Descriptive statistics and estimate variability	Treatment group	Abemaciclib +ET	ET	Hazard Ratio/ (P-value (2 sided) Stratified
	Number of subjects ITT Number of subjects Ki-67 index ≥20%	2808 1262	2829 1233	
	IDFS (number of events, n (%))	136 (4.8)	187 (6.6)	0.747 p=0.00957
	95% CI			(0.598, 0.932)
	Final IDFS Analysis			
Analysis population and time point description	Intent to treat, Final IDFS analysis			

Descriptive statistics and estimate variability	Treatment group	Abemaciclib +ET	ET	Hazard Ratio/ (P-value (2 sided) Stratified
	Number of subjects Ki-67 index ≥20% Number of subjects Ki-67 index ≥20% in Cohort 1	1262 1017	1236 986	
	IDFS Ki-67 index ≥20% (number of events, n (%))	82 (6.5)	115 (9.3)	0.691 p=0.01108
	95% CI			(0.519, 0.920)
	IDFS Ki-67 index ≥20% in Cohort 1 (number of events, n (%))	104 (10.2)	158 (16.0)	0.626 p= 0.0002
	95% CI			(0.488, 0.803)
	First OS Interim Analysis			
Analysis population and time point description	Intent to treat, first OS interim analysis			
Descriptive statistics and estimate variability	Treatment group	Abemaciclib +ET	ET	Hazard Ratio Stratified
	Number of subjects in Cohort 1	2555	2565	
	IDFS Cohort 1 (number of events, n (%))	218 (8.5)	318 (12.4)	0.680
	95% CI			(0.572, 0.808)
	DRFS Cohort 1 (number of events, n (%))	179 (7.0)	266 (10.4)	0.669
	95% CI			(0.554, 0.809)
	OS Cohort 1 (number of events, n (%))	90 (3.5)	88 (3.4)	1.044
	95% CI			(0.778, 1.401)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant provided data from a single open label phase 3 study, monarchE to support the proposed use of abemaciclib in combination with physician's choice of ET for treatment of patients with high risk, node positive, early stage, HR+, HER2-, breast cancer. High risk in monarchE was defined as either ≥ 4 pALN, or 1-3 pALN and at least one of the following criteria: tumour size ≥ 5 cm, histological grade 3 (Cohort 1); or Ki-67 ≥ 20 % (Cohort 2). However, the final proposed use of abemaciclib in

combination with ET only cover high risk defined as either ≥ 4 pALN, or 1-3 pALN and at least one of the following criteria: tumour size ≥ 5 cm or histological grade 3. This corresponds to patients in Cohort 1. A total of three DCOs have been presented.

5637 patients were randomized in the ITT population and 5120 patients were randomized in Cohort 1. The randomization was stratified by prior treatment (neoadjuvant chemotherapy vs adjuvant chemotherapy vs no chemotherapy), menopausal status (premenopausal vs postmenopausal at the time of diagnosis) and region (North America/Europe vs Asia vs Other). Eligibility criteria are considered acceptable and patient distribution, with regard to demographics, disease characteristics and prior medication and therapy were balanced between treatment groups.

Patients enrolled in Cohort 1 had a median age of 51.0 years and mean age was 52.2. 84.6% had an ECOG score of 0. Thirty-two (0.6%) of the 5120 patients were men. 50.5% had a tumour size measured by radiology prior to any systemic treatment of ≥20 mm - <50 mm, 18.6% had a tumour of ≥50 mm. 21.9% had 10 or more positive lymph nodes. Systemic therapy and radiotherapy were administered to the majority of the patients, 97.9% and 96.0% respectively before inclusion in the study.

Patient distribution, with regard to demographics, disease characteristics, and prior medication and therapy were balanced between treatment groups in Cohort 1.

The proportion of patients treated with bisphosphonates appears low considering that 56.6% of the women included were postmenopausal. By use of a less efficacious backbone therapy where bisphosphonates was not mandatory for postmenopausal women, the room for improvement by the add-on drug may potentially be increased compared with a more optimal backbone, inflating the effect size compared with what would be expected in clinical practice. The low use of adjuvant bisphosphonates may thus to some degree impact on the external validity of the results. To use of bisphosphonates during the study was also recommended in the advice. However, as the use is balanced between arms (Table 28), at least no important bias appears to be present in this regard.

There was a discrepancy between the proportion of premenopausal women and the proportion of patients receiving GnRH analogues. The menopausal status was reported at the time of the diagnosis and the choice of GnRH analogues was made at the start of adjuvant ET treatment. Menopausal status at the time when adjuvant ET was started was not recorded. This could at least partly explain the observed discrepancy. Considering that the frequency of patients with AI and TAM +/- GnRH analogues for pre- and postmenopausal women respectively was balanced across treatment arms, this is not expected to have had a major impact on interpretation of study results.

The primary objective of monarchE was to evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer for abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone. The primary efficacy analysis included a hierarchical test structure in the following listed order: IDFS in the ITT population, in the Ki-67 High population, in the Cohort 1 Ki-67 High population and OS of the ITT population. IDFS in the Cohort 2 population, with lower risk than Cohort 1 based on tumour spread, but classified as Ki-67 High, was an exploratory analysis. Secondary efficacy endpoints included DRFS and OS.

The endpoints (IDFS and DRFS) are considered acceptable, including IDFS as primary endpoint. However, as stated in the anti-cancer guideline 5th edition, the ultimate aim in the adjuvant setting is to increase the cure rate. In order to demonstrate cure rate and exclude a possible rebound effect when treatment is completed, a sufficiently long follow-up time after treatment completion is necessary. Reaching a plateau for survival may not occur in this setting as relapses have been

documented to occur for a very long time. 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 monarchE study. This has been reflected in the RMP and Annex II.

Several amendments and modifications were made to the study protocol, including changes related to the sample size, primary endpoint and analysis population, statistical plan, interim analyses, including timing and number of events and inclusion/exclusion criteria. In addition, all amendments were done after inclusion of patients had started. In principle, changes to pivotal analyses in an open label trial, where the outcome(s) of interest have reached more than negligible maturity, is a challenge to the type I error control.

The MAH assures that the changes performed to the SAP was not data driven and that procedures were in place to maintain the sponsor study team blinded. Acceptability of changes is contingent on the conclusion that they could not have been influenced by emerging data from the trial or that they have not changed the interpretation of trial results.

Therefore, a sensitivity analysis reverting to the original SAP, approved prior to first patient visit and before any unblinding safety analysis by the DMC was performed. The sensitivity analysis is based on the original SAP where the primary endpoint was IDFS in the ITT population, which was defined as the patients in Cohort 1. The primary endpoint of the original SAP meets the predefined IDFS primary endpoint at the second interim analysis. Thus, the study was considered positive at the second interim analysis according to the original SAP which is reassuring. The final IDFS analysis as defined in the initial SAP was performed at the first OS interim analysis and this did not deviate from the previous analysis.

The final design ensures control of the type 1-error for multiple interim analyses of the primary endpoint and the hypothesis testing of IDFS in multiple populations. OS can only be considered statistically significant once ITT, KI67H, C1-KI67H populations were all significant for IDFS. The plan was to perform the IDFS interim 2 analysis after 293 events, however there were a total of 323 IDFS events observed in the ITT population at the time of second IDFS interim analysis, including 136 patients in the A+ET arm and 187 patients in the ET only arm. This alters the significance level to be met for a positive efficacy conclusion. Based on the O'Brien-Fleming alpha spending function, this would require a two-sided p-value <0.0264 (p<0.0132, one-sided) according to the applicant.

In addition, the alpha spending function was changed in an amendment on 25 June 2019 from a fixed alpha level to using O'Brien-Fleming alpha spending. The timing (in terms of number of events) was altered accordingly.

The censoring rules to be applied for the time to event endpoints are presented but no other sensitivity or supplementary analyses to account for intercurrent events or missing data has been defined. Given the updated results based on a longer follow-up showing robust results sensitivity or supplementary analyses are not deemed necessary.

The rationale for conducting an open-label trial, based on experimental drug toxicity, is acknowledged. The measures described to maintain study integrity are considered standard. The open label design without independent review of endpoints means that investigator bias cannot be excluded. Given the nature of the endpoints in the current study, being hard endpoints with minimal likelihood of investigator bias in terms of the actual evaluation, this is considered a minor issue. However, the timing to the assessment was not governed by specific common time points at any time during the study and, for metastases, it was driven by the clinical need as per the investigator's judgement which potentially could be influenced by investigator expectations.

Efficacy data and additional analyses

The primary endpoint of IDFS was met for this study at the second IDFS interim analysis, demonstrating a statistically significant improvement (two-sided p=.0096) in IDFS for the ITT population with the A+ET arm compared to the ET only arm. Among 5637 randomized patients, a total of 323 IDFS events were observed in the ITT population at the time of second IDFS interim analysis, including 136 (4.8%) patients in the A+ET arm and 187 (6.6%) patients in the ET only arm. The estimated HR was 0.747 (95% CI: 0.598, 0.932). Efficacy in the ITT population was driven by the results in Cohort 1, efficacy in Cohort 2 have not been established.

At the final IDFS analysis statistical significance was also reached for Ki-67 High patients in the ITT population and in Cohort 1. Among the 2498 randomized patients with Ki-67 High in the ITT population, 197 IDFS events were observed, with 82 (6.5%) events in the A+ET arm and 115 (9.3%) events in the ET only arm (two-sided p=.001108 HR=0.691; 95% CI 0.519, 0.920). Among the 2003 randomized patients with Ki-67 High in Cohort 1, 177 IDFS events were observed, with 71 (7.0%) events in the A+ET arm and 106 (10.8%) events in the ET only arm (two-sided p=.00422 HR=0.643; 95% CI 0.475, 0.872). Efficacy in the Ki-67 High patient populations is driven by the results in Cohort 1, efficacy in Cohort 2 has not been established.

Further updates of efficacy data were requested due to the limited follow-up time presented for the second interim analysis of IDFS with approximately 15.5 months median follow-up time and the final IDFS analysis with approximately 19 months median follow-up time. This was provided with the first interim analysis of OS with a median follow-up of 27.7 months in Cohort 1. Median follow-up for patients off treatment was 6.0 months in Cohort 1. At this data cut-off, 73.3% of the patients had completed 2-years on study treatment and 17.4% discontinued early from the study treatment period. 8.5% of the patients were still on study treatment in Cohort 1.

A total of 536 IDFS events were observed in the Cohort 1 population at the first interim analysis for OS, including 218 (8.5%) events in the A+ET arm and 318 (12.4%) events in the ET only arm (HR=0.680, 95% CI: 0.572, 0.808). This effect magnitude is considered clinically relevant in agreement with precedent decisions.

At the first interim analysis for OS, IDFS in the Cohort 1 population displayed 24-months KM estimates of 92.6% in the A+ET arm and 89.6% in the ET only arm, indicating a 3.0% absolute improvement. The 36-months KM estimates of IDFS based on the first interim analysis of OS are 88.6% the A+ET arm and 82.9% in the ET only arm, indicating a 5.7% improvement. However, this 36-month estimate should be interpreted with caution due to the limited number of patients, 12.2 % in Cohort 1, that have been followed for at least 36 months.

In Cohort 1 efficacy in terms of IDFS and DRFS is considered established independently of Ki-67 status. For Ki-67 High patients in Cohort 1 a statistically significant IDFS result was observed. Ki-67 Low patients in Cohort 1 was an exploratory subgroup encompassing a total of 1914 patients. In this subgroup, at the first interim OS analysis 62 IDFS events (6.6%) were observed in the A+ET arm and 86 (8.9%) were observed in the ET only arm with a HR of 0.704 (95% Ci 0.506, 0.979). Efficacy can therefore be considered established independently of Ki-67 status in the high-risk population of Cohort 1, defined by clinicopathological features: ≥ 4 pALN or 1-3 pALN and tumour size ≥ 5 cm or; histological grade 3. The defined high-risk population is considered acceptable, based on the clinical argument of these clinicopathological features being both reliable and well-established.

Wide confidence intervals, small subgroup and immature data are issues encountered for the Cohort 2 population with only 1-3 pALN and Ki-67 High expression as additional high-risk features. These patients are included in the ITT and Ki-67 High ITT population. Disease characteristics for this patient population suggest a lower risk profile compared to Cohort 1 with less advanced tumour stage, fewer

patients with unfavourable histopathological grade at diagnosis and fewer positive lymph nodes. The possibility that the result presented for Cohort 2 is a chance finding due to the limited patient population and limited number of events was also considered.

While there is no reason to assume a different pharmaceutical impact on the target molecule in the tumours of patients in the different study cohorts, the absolute added efficacy of abemaciclib may still be lower in patients with better prognosis, for whom the backbone local therapy and systemic adjuvant endocrine therapy may in many cases be sufficient. In addition, inconsistencies in the methodology of assessment of Ki-67 and lack of golden standard guidelines are known to result in large variations of Ki-67 high positivity across laboratories, which question the general reliability of Ki-67 results and hamper the use of this marker in regulatory as well as clinical decision making. Updated IDFS results from the first interim analysis of OS from Cohort 2 (Table 32) displayed 14 (5.5%) events in the A +ET arm and 15 (5.7%) events in the ET only arm. The estimated HR was 0.986 (95% CI 0.475, 2.048). Taken together, efficacy has not been established in this subgroup.

Subgroup analyses of IDFS and DRFS in Cohort 1, other than Ki-67, suggest that benefit was observed across the predefined subgroups of reasonable size.

Subgroup results for the different classes of ET were provided for IDFS and DRFS based on the first interim analysis of OS with DCO 1 April 2021 for the Cohort 1 population. Frequency of IDFS and DRFS events and HR favours abemaciclib addition regardless of backbone ET. The 95% CI for IDFS and DRFS rate at 2 years per treatment arm is overlapping, as well as the 95% CI for HR per treatment arm for each backbone ET for IDFS and DRFS.

Treatment with abemaciclib + ET compared to only ET conferred a numerical benefit in DRFS supporting the positive outcome of IDFS.

The OS data is too immature for all presented data cut-offs to draw any conclusion of the effect of abemaciclib on OS. At the first interim analysis for OS there were 178 deaths in the Cohort 1 population: 90 deaths (3.5 %) in the A+ET arm, and 88 deaths (3.4%) in the ET only arm. The estimated HR of OS was 1.044 (95% CI 0.778, 1.401). This represents a substantial uncertainty of the effect on survival of adjuvant abemaciclib added to ET for patients with high-risk early breast cancer. In addition, the follow-up time (27.7 months median follow-up time and 6.0 months median follow-up off treatment) is still relatively limited given the known relapse pattern of HR+ breast cancer, precluding exact estimates of the clinical efficacy endpoints in a longer-term perspective. However, considering that over 90% of the patients have discontinued study treatment, the number of deaths related to drug toxicity is likely to drop. Conversely, the number of deaths due to metastatic disease will, for both arms, increase over time. Given the effects of the abemaciclib addition on both disease recurrence and distant recurrences (IDFS and DRFS), the OS results may therefore be expected to improve with longer follow-up, and may at least be expected not to be detrimental for the addition of abemaciclib to standard ET for the high-risk population defined in Cohort 1. The applicant has committed to submit 5-year follow-up for efficacy and safety including OS data in the final study report for the monarchE study. This has been reflected in the RMP and Annex II.

For the assessment of health outcome and quality of life, the timing of the assessments did not allow to capture the effects of any AEs the patient might have experienced during the first 3 months. This is considered a limitation.

The mean scores and changes from baseline scores appear similar in both arms for FACT-B, EACT-ES, EQ-5D-5L index and VAS scores in the ITT population. However, due to the open-label, the presented data should be interpreted with caution. Moreover, any equivalence claim presupposes the sensitivity

of the assays as used in the trial to show a difference if there was not; this cannot be ascertained in the absence of a difference. Therefore, firm conclusions of quality of life with abemaciclib as additive treatment to ET cannot be drawn.

2.4.3. Conclusions on the clinical efficacy

The pivotal study is formally positive according to its final SAP. Updated analyses with 27.7 months follow up in Cohort 1, which is considered sufficient to establish efficacy, indicate an effect on IDFS in Cohort 1 that would be deemed clinically relevant based on precedent decisions. The high-risk population in Cohort 1 is defined by well-known and established clinicopathological high risk features: ≥4pALN or 1-3 pALN and tumour size ≥5 cm or histological grade 3.

There is remaining uncertainty about the impact of Verzenios on OS, due to immature data. The HR in Cohort 1 is 1.044 (0.778, 1.401) underlining that efficacy in terms of OS has not been established. The number of deaths attributed to study disease was 68 for patients treated with abemaciclib +ET and 73 for patients treated with ET. The number of deaths attributed to adverse events are in total 21 (0,82%) for patients treated with abemaciclib +ET and 14 (0.55%) for patients treated with ET in Cohort 1. However, the risk of deaths due to AEs is unlikely to increase as more than 90% of patients have discontinued therapy, while the number of deaths due to recurrent metastatic disease (distant relapse) will increase. With longer follow-up it is therefore considered probable that the absolute difference in DRFS of 3.4% observed in Cohort 1 will translate into at least a non-detrimental OS.

There is a need for further follow-up of overall survival and the temporal pattern of relapse. 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 monarchE study. This has been reflected in the RMP and Annex II.

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

Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy and safety of Verzenios in combination with endocrine therapy for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence, the MAH should submit a 5-year follow-up of the monarchE study.

2.5. Clinical safety

Introduction

The submitted summary of clinical safety for the currently applied indication, early breast cancer (EBC), describes the results of the pre-planned interim analysis 2 (IA2) of study monarchE, with the data cutoff date of 16 March 2020. During the course of the assessment, updated safety data were submitted from the final IFDS analysis (data cutoff 8 July 2020) and the OS IA1 analysis (data cutoff April 2021).

Patient exposure

All patients included in monarchE who received at least one dose of any study therapy were evaluated for safety and toxicity.

Among the 5637 randomised patients, 5591 patients were treated with at least one dose of study treatment and thus included in the safety population. This included 2791 patients in the A+ET arm and 2800 patients in the ET only arm.

Patients were planned to complete a maximum of 24 months of treatment. Duration of study treatment at OS IA1 is summarised in Table 47.

Among patients in the A+ET arm, 72% had at least 1 dose modification (dose omission or dose reduction).

Dose omissions were made in 1908 (68%) of patients in the abemaciclib arm.

Per protocol, a maximum of 2 dose reductions was allowed, first to 100 mg twice daily and thereafter to 50 mg twice daily. Approximately 44% of patients in the A+ET arm had at least one dose reduction, and 14% had two dose reductions. Almost all were due to AEs.

The reasons for treatment discontinuation and dose modifications are further discussed in section 'Discontinuations and dose modifications due to AEs' below.

Table 47. Duration of Drug Exposure (April 2021 cut-off)

	LY2835219-150mg + EDT N=2791		EDT N=2800
Number (%) of Patients	Abemaciclib 2783 (99.7)	Endocrine 2791 (100.0)	Endocrine 2799 (100.0)
Cycles received per patient *a			
Median	24.00	25.00	25.00
Q1-Q3	17.00 - 25.00	24.00 - 25.00	24.00 - 25.00
Min-Max	1.00 - 28.00	1.00 - 29.00	1.00 - 29.00
Mean	19.76	21.70	22.21
Std Dev.	8.30	6.83	6.07
Duration of Therapy (Weeks)			
Median	102.71	103.00	103.00
Q1-Q3	72.14 - 103.14	99.29 - 103.43	100.00 - 103.29
Min-Max	0.14 - 117.14	0.14 - 124.14	0.14 - 122.00
Mean	82.32	90.56	92.68
Std Dev.	35.32	29.05	25.93

Abbreviations: max=maximum, min=minimum; N=number of patients in safety population;
Q1-Q3=Quarter 1- Quarter 3, interquartile range; SD=standard deviation;
*a Cycles in this analysis are defined as every 30 days of treatment

Study population

The demographics of the study population is described in Table 20 above (under Clinical Efficacy).

The most common pre-existing conditions are summarised in Table 48.

Table 48. Summary of Pre-existing Conditions in Greater than or Equal to 5% of the study population

System Organ Class, n (%) Preferred Term	Arm A Abemaciclib + ET N=2791	Arm B ET N=2800	Total N=5591
Patients with ≥1 preexisting condition[a]	2203 (78.9)	2206 (78.8)	4409 (78.9)
Vascular disorders	1031 (36.9)	1085 (38.8)	2116 (37.8)
Hypertension	662 (23.7)	671 (24.0)	1333 (23.8)
Hot flush	290 (10.4)	367 (13.1)	657 (11.8)
Musculoskeletal and connective tissue disorders	738 (26.4)	817 (29.2)	1555 (27.8)
Arthralgia	250 (9.0)	301 (10.8)	551 (9.9)
Nervous system disorders	634 (22.7)	698 (24.9)	1332 (23.8)
Neuropathy peripheral	222 (8.0)	252 (9.0)	474 (8.5)
Psychiatric disorders	576 (20.6)	595 (21.3)	1171 (20.9)
Insomnia	247 (8.8)	234 (8.4)	481 (8.6)
Depression	231 (8.3)	222 (7.9)	453 (8.1)
Anxiety	201 (7.2)	196 (7.0)	397 (7.1)
Metabolism and nutrition disorders	568 (20.4)	575 (20.5)	1143 (20.4)
Gastrointestinal disorders	513 (18.4)	512 (18.3)	1025 (18.3)
Gastrointestinal reflux disease	157 (5.6)	155 (5.5)	312 (5.6)
General disorders and administration site conditions	378 (13.5)	447 (16.0)	825 (14.8)
Fatigue	254 (9.1)	281 (10.0)	535 (9.6)
Skin and subcutaneous tissue disorders	330 (11.8)	352 (12.6)	682 (12.2)
Endocrine disorders	323 (11.6)	320 (11.4)	643 (11.5)
Hypothyroidism	225 (8.1)	226 (8.1)	451 (8.1)
Injury, poisoning and procedural complications	273 (9.8)	257 (9.2)	530 (9.5)
Radiation skin injury	194 (7.0)	185 (6.6)	379 (6.8)
Immune system disorders	263 (9.4)	273 (9.8)	536 (9.6)
Respiratory, thoracic and mediastinal disorders	257 (9.2)	273 (9.8)	530 (9.5)
Cardiac disorders	166 (5.9)	157 (5.6)	323 (5.8)
Reproductive system and breast disorders	166 (5.9)	202 (7.2)	368 (6.6)
Benign prostatic hyperplasia[b]	3 (14.3)	2 (13.3)	5 (13.9)
Hepatobiliary disorders	140 (5.0)	157 (5.6)	297 (5.3)

Adverse events

An overview of adverse events in monarchE is presented in Table 49.

The incidence of all grade and Grade ≥3 TEAEs reported was higher in the A+ET arm compared to the ET only arm. Similarly, there were more patients who experienced a treatment-emergent SAE and discontinued study treatment due to an AE or SAE in the A+ET arm versus the ET only arm. However, the higher incidence of Grade ≥3 TEAEs in the A+ET arm (> 3 times higher than in the ET only arm) did not translate into a proportionally higher rate of SAEs (< 2 times higher than in the ET only arm).

Table 49. Overview of Adverse Events by data cutoff (Safety population)

	Abemaciclib + ET N = 2791, n (%)		ET Alone N = 2800, n (%)	
	Final IDFS[a]	OS IA1[b]	Final IDFS[a]	OS IA1[b]
Patients with ≥1 TEAE	2733 (97.9)	2745 (98.4)	2441 (87.2)	2486 (88.8)
Patients with ≥1 CTCAE Grade ≥ 3 TEAE	1323 (47.4)	1388 (49.7)	397 (14.2)	456 (16.3)
Patients with ≥1 TE-SAE	372 (13.3)	424 (15.2)	219 (7.8)	247 (8.8)
Patients who discontinued abemaciclib due to AE	481 (17.2)	515 (18.5)	NA	NA
Patients who discontinued all study treatment due to AE	172 (6.2)[c]	181 (6.5)[d]	23 (0.8)	30 (1.1)
Patients who died due to AE on study therapy or ≤30 days of discontinuation from study treatment	11 (0.4)	15 (0.5)	9 (0.3)	10 (0.4)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; IDFS = invasive disease-free survival; N = number of patients in the ITT population; n = number of patients in the specific population; OS IA1 = Overall Survival Interim Analysis 1; TEAE = treatment-emergent adverse events, TE-SAE = treatment-emergent serious adverse event.

[a] Data cutoff: 08 July 2020.

[b] Data cutoff: 01 April 2021.

[c] The 6.2% is included in the 17.2% of patients who discontinued abemaciclib due to AE. Patients could continue their ET as post-discontinuation therapy.

[d] The 6.5% is included in the 18.5% of patients who discontinued abemaciclib due to AE. Patients could continue their ET as post-discontinuation therapy.

TEAEs by SOC

Gastrointestinal disorders were the most common TEAEs in the A+ET arm (around 90%), followed by blood and lymphatic system disorders (around 60%) and general disorders and administration site conditions (around 55%).

For gastrointestinal disorders, the most frequently reported TEAEs with at least 20% incidence in the A+ET arm were:

- diarrhoea
- abdominal pain
- nausea

For blood and lymphatic system disorders, the most frequently reported (>20%) TEAEs for the A+ET arm were:

- neutropenia
- leukopenia
- anaemia

TEAEs by CTCAE grade and PTs

TEAEs by maximum CTCAE grade and PT that occurred in greater than or equal to 10% of patients in either arm, in order of decreasing frequency are summarised in Table 50.

The most common Grade ≥3 TEAEs (>2.0%) in the A+ET arm included neutropenia, leukopenia, diarrhoea, lymphopenia, and fatigue.

Table 50. Treatment-Emergent Adverse Events by Maximum CTCAE Grade, Preferred Term by Decreasing Frequency (All Grades) (April 2021 data cutoff)

	Arm A LY2835219-150mg+EDT (N=2791)					Arm B EDT (N=2800)				
	CTCAE Grade, n (%)					CTCAE Grade, n (%)				
Preferred Term	1	2	3	>=3	Any Grade	1	2	3	>=3	Any Grade
Subjects with >=1 TEAE	165 (5.9)	1192 (42.7)	1284 (46.0)	1388 (49.7)	2745 (98.4)	634 (22.6)	1396 (49.9)	424 (15.1)	456 (16.3)	2486 (88.8)
Diarrhoea	1255 (45.0)	857 (30.7)	218 (7.8)	219 (7.8)	2331 (83.5)	184 (6.6)	52 (1.9)	6 (0.2)	6 (0.2)	242 (8.6)
Neutropenia	178 (6.4)	554 (19.8)	527 (18.9)	546 (19.6)	1278 (45.8)	66 (2.4)	68 (2.4)	19 (0.7)	23 (0.8)	157 (5.6)
Fatigue	632 (22.6)	421 (15.1)	80 (2.9)	80 (2.9)	1133 (40.6)	378 (13.5)	117 (4.2)	4 (0.1)	4 (0.1)	499 (17.8)
Leukopenia	170 (6.1)	562 (20.1)	313 (11.2)	317 (11.4)	1049 (37.6)	93 (3.3)	82 (2.9)	11 (0.4)	11 (0.4)	186 (6.6)
Abdominal pain	693 (24.8)	260 (9.3)	39 (1.4)	39 (1.4)	992 (35.5)	189 (6.8)	77 (2.8)	9 (0.3)	9 (0.3)	275 (9.8)
Nausea	623 (22.3)	187 (6.7)	14 (0.5)	14 (0.5)	824 (29.5)	198 (7.1)	52 (1.9)	2 (0.1)	2 (0.1)	252 (9.0)
Arthralgia	509 (18.2)	224 (8.0)	9 (0.3)	9 (0.3)	742 (26.6)	729 (26.0)	302 (10.8)	29 (1.0)	29 (1.0)	1060 (37.9)
Anaemia	383 (13.7)	241 (8.6)	56 (2.0)	57 (2.0)	681 (24.4)	75 (2.7)	19 (0.7)	9 (0.3)	10 (0.4)	104 (3.7)
Headache	415 (14.9)	123 (4.4)	8 (0.3)	8 (0.3)	546 (19.6)	321 (11.5)	95 (3.4)	5 (0.2)	5 (0.2)	421 (15.0)
Vomiting	375 (13.4)	101 (3.6)	15 (0.5)	15 (0.5)	491 (17.6)	98 (3.5)	29 (1.0)	3 (0.1)	3 (0.1)	130 (4.6)
Hot flush	326 (11.7)	97 (3.5)	4 (0.1)	4 (0.1)	427 (15.3)	496 (17.7)	137 (4.9)	10 (0.4)	10 (0.4)	643 (23.0)
Lymphopenia	75 (2.7)	169 (6.1)	148 (5.3)	151 (5.4)	395 (14.2)	38 (1.4)	45 (1.6)	13 (0.5)	13 (0.5)	96 (3.4)
Cough	310 (11.1)	80 (2.9)	1 (0.0)	1 (0.0)	391 (14.0)	177 (6.3)	45 (1.6)	0 (0.0)	0 (0.0)	222 (7.9)
Stomatitis *a	309 (11.1)	72 (2.6)	4 (0.1)	4 (0.1)	385 (13.8)	133 (4.8)	18 (0.6)	0 (0.0)	0 (0.0)	151 (5.4)
Thrombocytopenia	276 (9.9)	61 (2.2)	28 (1.0)	36 (1.3)	373 (13.4)	40 (1.4)	8 (0.3)	2 (0.1)	4 (0.1)	52 (1.9)
Lymphoedema	258 (9.2)	84 (3.0)	5 (0.2)	5 (0.2)	347 (12.4)	204 (7.3)	45 (1.6)	1 (0.0)	1 (0.0)	250 (8.9)
Alanine aminotransferase increased	184 (6.6)	82 (2.9)	72 (2.6)	77 (2.8)	343 (12.3)	113 (4.0)	25 (0.9)	19 (0.7)	19 (0.7)	157 (5.6)
Urinary tract infection	2 (0.1)	318 (11.4)	16 (0.6)	16 (0.6)	336 (12.0)	0 (0.0)	205 (7.3)	6 (0.2)	6 (0.2)	211 (7.5)
Constipation	282 (10.1)	49 (1.8)	2 (0.1)	2 (0.1)	333 (11.9)	144 (5.1)	23 (0.8)	1 (0.0)	1 (0.0)	168 (6.0)
Aspartate aminotransferase increased	220 (7.9)	58 (2.1)	49 (1.8)	52 (1.9)	330 (11.8)	103 (3.7)	19 (0.7)	15 (0.5)	15 (0.5)	137 (4.9)
Decreased appetite	243 (8.7)	70 (2.5)	16 (0.6)	16 (0.6)	329 (11.8)	53 (1.9)	13 (0.5)	2 (0.1)	2 (0.1)	68 (2.4)
Alopecia	283 (10.1)	30 (1.1)	0 (0.0)	0 (0.0)	313 (11.2)	68 (2.4)	7 (0.3)	0 (0.0)	0 (0.0)	75 (2.7)
Rash	239 (8.6)	61 (2.2)	11 (0.4)	11 (0.4)	312 (11.2)	104 (3.7)	23 (0.8)	0 (0.0)	0 (0.0)	127 (4.5)
Blood creatinine increased	241 (8.6)	67 (2.4)	3 (0.1)	3 (0.1)	311 (11.1)	19 (0.7)	4 (0.1)	0 (0.0)	0 (0.0)	23 (0.8)
Dizziness	270 (9.7)	30 (1.1)	4 (0.1)	4 (0.1)	304 (10.9)	167 (6.0)	20 (0.7)	1 (0.0)	1 (0.0)	188 (6.7)
Upper respiratory tract infection	0 (0.0)	295 (10.6)	6 (0.2)	6 (0.2)	301 (10.8)	1 (0.0)	237 (8.5)	0 (0.0)	0 (0.0)	238 (8.5)
Pain in extremity	205 (7.3)	78 (2.8)	3 (0.1)	3 (0.1)	286 (10.2)	251 (9.0)	70 (2.5)	4 (0.1)	4 (0.1)	325 (11.6)
Back pain	192 (6.9)	81 (2.9)	10 (0.4)	10 (0.4)	283 (10.1)	230 (8.2)	108 (3.9)	9 (0.3)	9 (0.3)	347 (12.4)
Pyrexia	229 (8.2)	48 (1.7)	2 (0.1)	2 (0.1)	279 (10.0)	102 (3.6)	25 (0.9)	0 (0.0)	0 (0.0)	127 (4.5)

*a Terms include Stomatitis, Mucosal inflammation, Mouth ulceration, Oropharyngeal pain

The AE profile in EBC was overall similar to that previously observed in MBC. A few new ADRs for inclusion in section 4.8 of the SmPC were identified (headache, dyspepsia, stomatitis, nail disorders). On the other hand, some ADRs observed in MBC were not considered ADRs for inclusion in section 4.8 in the EBC population (febrile neutropenia, dry skin, muscular weakness, pyrexia) or occurred at a lower frequency than in the MBC population (alopecia, pruritus, rash, ALT increased, AST increased).

Hot flush and arthralgia were more commonly reported in the EBC population than in the MBC population. This was suggested due to the EBC population being younger (median age 51 years). These are known ADRs for endocrine therapy, and occurred at higher frequency in the ET only arm than in the A+ET arm.

Serious adverse event/deaths/other significant events

Deaths

An overall summary of the deaths in study monarchE is shown in Table 51.

Table 51. Summary of Deaths at the Time of the OS IA1 analysis (April 2021 cut-off)

n (%)	**Arm A Abemaciclib + ET N=2791**	**Arm B ET N=2800**
All deaths	95 (3.4)	89 (3.2)
Deaths on therapy or ≤30 days from discontinuation of study treatment	21 (0.8)	19 (0.7)
Reasons for death		
Study disease	6 (0.2)	9 (0.3)
Adverse events	15 (0.5)	10 (0.4)
Deaths occurring >30 days from study treatment discontinuation	74 (2.7)	70 (2.5)
Reasons for death		
Study disease	65 (2.3)	66 (2.4)
Adverse events	9 (0.3)	4 (0.1)

Abbreviations: ET = endocrine therapy; N = number of patients in the safety population; n = number of patients in the specific category.
Data cutoff: 01 April 2021.

There were 95 deaths in the A+ET arm (3.4%) and 89 in the ET only arm (3.2%). Most fatalities were due to study disease.

There were, however, 24 and 14 deaths due to AEs in the A+ET arm and the ET only arm, respectively, of which 15 and 10, respectively, occurred during or within 30 days from discontinuation of treatment. Thus, there were more deaths due to AEs in the A+ET arm than in the ET only arm. Most of the deaths on the A+ET arm were confounded with significant comorbid conditions/medical history.

The disposition of the reported deaths is summarised in Table 52.

Table 52. Summary of Deaths by System Organ Class and Preferred Terms Safety Population (April 2021 cut-off)

n (%)	Arm A Abemaciclib + ET N=2791	Arm B ET N=2800
All deaths	**95 (3.4)**	**89 (3.2)**
Deaths on therapy or ≤30 days from discontinuation of study treatment	**21 (0.8)**	**19 (0.7)**
Reasons for death		
Study disease	**6 (0.2)**	**9 (0.3)**
Adverse events, PT within SOC	**15 (0.5)**	**10 (0.4)**
Cardiac disorders	**5 (0.2)**	**0**
Cardiac arrest	1 (0.0)	0
Cardiac failure	2 (0.1)	0
Myocardial infarction	1 (0.0)	0
Ventricular fibrillation	1 (0.0)	0
Gastrointestinal disorders	**2 (0.1)**	**0**
Diarrhea	1 (0.0)	0
Mesenteric artery thrombosis	1 (0.0)	0
General disorders and administrative site conditions	**1 (0.0)**	**2 (0.1)**
General physical health deterioration	1 (0.0)	0
Death	0	1 (0.0)
Sudden death	0	1 (0.0)
Infections and infestations	**3 (0.1)**	**5 (0.2)**
COVID-19 pneumonia	1 (0.0)	1 (0.0)
Suspected COVID-19	1 (0.0)	0
Influenza	0	1 (0.0)
Pneumonia	1 (0.0)[a]	1 (0.0)
Septic shock	0	1 (0.0)
Urosepsis	0	1 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (0.0)**
Gastrointestinal adenocarcinoma	0	1 (0.0)
Nervous system disorders	**2 (0.1)**	**0**
Cerebral hemorrhage	1 (0.0)	0
Cerebrovascular accident	1 (0.0)	0
Respiratory, thoracic and mediastinal disorders	**2 (0.1)**	**2 (0.1)**
Hypoxia	1 (0.0)	0
Pneumonitis	1 (0.0)	0
Pulmonary embolism	0	1 (0.0)
Pleural effusion	0	1 (0.0)
Deaths occurring >30 days from study treatment discontinuation	**74 (2.7)**	**70 (2.5)**
Reasons for death		
Study disease	**65 (2.3)**	**66 (2.4)**
Adverse events, PT within SOC	**9 (0.3)**	**4 (0.1)**

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (0.1)**	**1 (0.0)**
Colon cancer	1 (0.0)	0
Colon cancer metastatic	1 (0.0)	0
Myelodysplastic syndrome	1 (0.0)	0
Malignant neoplasm of ampulla of Vater	0	1 (0.0)
Gastrointestinal disorders	**0**	**1 (0.0)**
Diverticular perforation	0	1 (0.0)
Injury, poisoning and procedural complications	**1 (0.0)**	**0**
Subdural hematoma	1 (0.0)	0
General disorders and administrative site conditions	**3 (0.1)**	**0**
Death	3 (0.1)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.0)**	**1 (0.0)**
Respiratory failure	0	1 (0.0)
Pulmonary embolism	1 (0.0)	0
Psychiatric disorders	**0**	**1 (0.0)**
Completed Suicide	0	1 (0.0)
Infections and infestations	**1 (0.0)**	**0**
COVID-19	1 (0.0)	0

[a] Reported term lung infection (suspected COVID-19).

The main differences between the treatment arms were deaths due to cardiac disorders in the A+ET arm and infections/infestations (other than Covid-19) in the ET only arm. However, there were more deaths due to Covid-19 or suspected Covid-19 in the A+ET arm than in the ET only arm (4 versus 1).

The 5 patients in the A+ET arm who died due to reasons in the SOC cardiac disorders, all had significant relevant medical history and/or cardiovascular risk factors. There was no specific etiology or pattern for the deaths. Two of these patients discontinued abemaciclib (while ET was continued) more than 30 days prior to death. The cases of death due to cardiac disorders are briefly described below:

- Cardiac arrest – 68-year old women, previous smoker with hypertension. Previous systemic therapy: cyclophosphamide, doxorubicin, paclitaxel. Time to onset (TTO) was 12 months.
- Cardiac failure 1 – 82-year old woman. Her medical history included hypertension, diabetes mellitus, obesity, former tobacco use, former alcohol use, cerebrovascular accident, atrial fibrillation, electrocardiogram QT prolonged, asthma and hypertriglyceridemia, Gr 3 chronic renal disease. Previous systemic therapy: letrozole. The cause of the event was thought to be worsening of the renal disease and lung oedema. The patient received only 9 doses of abemaciclib, where after it was stopped due to fatigue. Her condition worsened a few days later, and death occurred about 2 months later.
- Cardiac failure 2 – 82-year old woman. Her medical history included congestive heart failure (CHF), atrial fibrillation, hypertension, hyperlipidaemia, cardiomegaly, chronic obstructive pulmonary disease (COPD), coronary artery disease, coronary stent and pacemaker. Relevant significant medications included amlodipine, hydralazine for hypertension; furosemide, metoprolol for congestive heart failure. Previous chemotherapy: none. The TTO in this case was 13 months.
- Myocardial infarction – 63-year old woman. The TTO after start of abemaciclib was 9 months, but the patient had discontinued abemaciclib 2 months before the event due to fatigue. She suffered from type II diabetes mellitus (treated with metformin and insulin glargine). Previous systemic therapy: paclitaxel, 5-fluorouracil, cyclophosphamide. The event was considered due to uncontrolled diabetes.

- Ventricular fibrillation and cardiac arrest – 64-year old woman. Her medical history included coronary artery disease, hypertension, hyperlipidemia and type 2 diabetes mellitus (treated with metformin and insulin lispro). Previous systemic therapy included: cyclophosphamide, doxorubicin, paclitaxel. The event was considered due to anatomically severe coronary artery disease. TTO was 12 months.

A more in-depth review of cardiac disorders reported in association with abemaciclib treatment in Phase 3 trials and post-marketing reports did not indicate discernible pattern among the cardiac events reported at abemaciclib treatment. The most common SAE within the SOC cardiac disorders was atrial fibrillation, which did not indicate a common etiology with the cardiac deaths reported in monarchE.

At the time of the Final IDFS analysis, there were no fatal AEs due to infection in the A+ET arm versus 4 in the ET only arm (influenza, pneumonia, septic shock, urosepsis). At OS IA1, there were 4 additional fatal AEs due to infection in the A+ET arm and 1 additional fatal AE due to infection in the ET only arm. All these additional fatal AEs were due to COVID-19 or suspected COVID-19, including a fatal AE reported as 'pneumonia' in the A+ET arm (Table 52).

Of the 4 deaths due to COVID-19 or suspected COVID-19 in the A+ET arm, 2 patients had relevant risk factors such as hypertension, angiopathy, and obesity, which may have contributed to a more severe form of the disease. One patient died due to COVID-19 pneumonia in the ET only arm**,** with a history of asthma and atrial fibrillation. The timing of the COVID-19 associated deaths is reflective of the pandemic evolution, with the highest global incidence occurring at the end of the 2-year treatment period for patients still on treatment.

The two deaths due to Nervous system disorders in the A+ET arm were reported as cerebral haemorrhage and cerebrovascular accident, respectively. In the latter case the patient reportedly fell on the stairs, hitting her head. The one remaining case was by autopsy confirmed as acute vascular pathology.

Fatal AEs in the Respiratory, Thoracic, and Mediastinal System Disorders SOC accounts for deaths in 2 patients each in the A+ET arm and the ET only arm. One patient in the A+ET arm died of 'hypoxia' after a femoral arterial thrombectomy while on a respirator. Another patient in the A+ET arm, with a history of radiotherapy 3 weeks prior to randomization, was hospitalized with severe pneumonitis 3 months after starting treatment with abemaciclib and anastrozole and died 48 days after the last dose of abemaciclib. One patient in the ET only arm died of pulmonary embolism after a recurrence of breast cancer, while on letrozole for approximately 5.5 months. Another patient in the ET only arm died of pleural effusion due to lymphedema, after approximately 20.5 months on treatment with anastrozole.

There were 3 deaths due to AE non-breast neoplasm in the A+ET arm (colon cancer, metastatic colon cancer, squamous cell carcinoma of the lung, myelodysplastic syndrome), and 2 deaths due to non-breast neoplasm in the ET only arm. In addition, there was one case in the A+ET arm reported as "Death" (reason not specified) that was considered likely due to the patient's second primary neoplasm squamous cell carcinoma of the lung.

Deaths with other causes that occurred during or within 30 days after discontinuation of treatment in the abemaciclib + ET arm included:

- One 84-year-old patient with a history of hypertension and type 2 diabetes mellitus was treated for approximately 7 months with abemaciclib plus letrozole and died of unclear intra-abdominal pathology (reported term 'diarrhoea') 2 days after the discontinuation of all study treatment. No autopsy was performed but the ICU physician suggested the cause of death was abdominal sepsis. The Investigator instead suggested the diarrhoea was a symptom of mesenteric ischemia, which

was considered probably not related to abemaciclib, although it could not be ruled out that the mesenteric ischemia was due to thrombosis caused by abemaciclib.
- One 79-year-old patient with a history of atrial fibrillation and arterial thrombotic disease, complicated by a history of hypertension, diabetes mellitus, coronary artery bypass graft (12 years prior to event), and a recent stent placement due to a coronary occlusion, died following ischemic intestinal disease due to mesenteric artery thrombosis, 18 months after starting study treatment with abemaciclib and anastrozole. The event was considered consistent with the patient's age and medical history.
- One 62-year-old patient with a history of chronic renal failure and metabolic syndrome (obesity + hypertension + insulin resistance) died of general physical health deterioration after being transferred to a nephrology unit due to an exacerbation of pre-existing chronic renal failure. This patient received study treatment of abemaciclib plus letrozole for 20.5 months and died 5 days after the last dose of abemaciclib.

Deaths with 'other causes' occurring **> 30 days after discontinuation** of study treatment in the A+ET arm included:

- subdural haematoma after a fall
- death due to unknown cause (10.5 months after discontinuation) but considered likely due to underlying cirrhosis
- death due to unknown cause, as the family refused to provide information (19 months after discontinuation). The patient had been diagnosed with myelodysplastic syndrome 5 month after discontinuation of study treatment
- death due to unknown cause, but considered likely due to complications of underlying malignancy - the patient was diagnosed with squamous cell carcinoma of the lung approximately 1.5 years after starting study treatment, discontinued all study treatment due to study disease relapse, and died approximately 6 months later.
- pulmonary embolism. The patient was receiving carboplatin in the context of metastatic disease (lung) at the time of death.

In summary, it appears to be no particular temporal pattern and, except for deaths due to COVID-19, no pattern or common underlying pathophysiological cause of death in either treatment arm. None of the deaths due to AEs, in either treatment arm, were considered related to study treatment, with the possible exception of one death reported due to 'diarrhoea', but for which the cause could not be decided.

Other serious adverse events

Treatment-emergent SAEs occurring in ≥ 5 patients are summarised in Table 53. The overall incidence of SAEs was higher in patients in the A+ET arm (12.3%) compared with the ET only arm (7.2%).

Table 53. Treatment-Emergent Serious Adverse Events Occurring in Greater than or Equal to 5 Patients in Any Arm, Preferred Term by Decreasing Frequency in the A+ET arm (Apr 2021 cut-off)

Preferred Term	LY2835219-150 mg+EDT (N=2791) n (%)	EDT (N=2800) n (%)	Total (N=5591) n (%)
Subjects >= 1 Serious Adverse Events	424 (15.2)	247 (8.8)	671 (12.0)
Pneumonia	28 (1.0)	17 (0.6)	45 (0.8)
Pulmonary embolism	18 (0.6)	4 (0.1)	22 (0.4)
Deep vein thrombosis	16 (0.6)	4 (0.1)	20 (0.4)
Diarrhoea	15 (0.5)	0 (0.0)	15 (0.3)
Cellulitis	14 (0.5)	10 (0.4)	24 (0.4)
Urinary tract infection	14 (0.5)	4 (0.1)	18 (0.3)
Cholecystitis	10 (0.4)	4 (0.1)	14 (0.3)
Pyrexia	10 (0.4)	0 (0.0)	10 (0.2)
COVID-19 pneumonia	9 (0.3)	1 (0.0)	10 (0.2)
Anaemia	8 (0.3)	2 (0.1)	10 (0.2)
Atrial fibrillation	8 (0.3)	1 (0.0)	9 (0.2)
Pneumonitis	8 (0.3)	0 (0.0)	8 (0.1)
Dehydration	7 (0.3)	0 (0.0)	7 (0.1)
Influenza	7 (0.3)	4 (0.1)	11 (0.2)
Lymphoedema	7 (0.3)	3 (0.1)	10 (0.2)
Abdominal pain	6 (0.2)	1 (0.0)	7 (0.1)
Acute kidney injury	6 (0.2)	1 (0.0)	7 (0.1)
Appendicitis	6 (0.2)	2 (0.1)	8 (0.1)
Erysipelas	6 (0.2)	0 (0.0)	6 (0.1)
Mastitis	6 (0.2)	7 (0.3)	13 (0.2)
Pancreatitis	6 (0.2)	2 (0.1)	8 (0.1)
Sepsis	6 (0.2)	2 (0.1)	8 (0.1)
Thrombocytopenia	6 (0.2)	1 (0.0)	7 (0.1)
Upper respiratory tract infection	6 (0.2)	0 (0.0)	6 (0.1)
Alanine aminotransferase increased	5 (0.2)	1 (0.0)	6 (0.1)
Aspartate aminotransferase increased	5 (0.2)	1 (0.0)	6 (0.1)
Breast cellulitis	5 (0.2)	5 (0.2)	10 (0.2)
Cholecystitis acute	5 (0.2)	0 (0.0)	5 (0.1)
Colitis	5 (0.2)	3 (0.1)	8 (0.1)
Febrile neutropenia	5 (0.2)	0 (0.0)	5 (0.1)
Nephrolithiasis	5 (0.2)	2 (0.1)	7 (0.1)
Syncope	5 (0.2)	2 (0.1)	7 (0.1)
Diverticulitis	3 (0.1)	5 (0.2)	8 (0.1)
Wound dehiscence	0 (0.0)	5 (0.2)	5 (0.1)

Abbreviations: N = number of subjects in the analysis population; n = number of subjects with events meeting specified criteria.

The most frequent cause of SAEs in the A+ET arm by SOC were infections and infestations followed by gastrointestinal disorders.

The most common SAEs in the A+ET arm were reported under the composite term *venous thromboembolic events* (*VTEs)* and pneumonia.

Patients entered long-term follow-up 30 days after study treatment discontinuation. Patients were monitored in long-term follow-up for SAEs, regardless of causality attribution, to detect any long-term serious toxicities which are relevant for the adjuvant setting.

During the long-term follow-up period, at least 1 SAE was reported for 84 patients, 38 in the A+ET arm (1.4%) and 46 in the ET only arm (1.6%). The most common causes (5 or more patients) of SAEs in long-term follow-up by SOC were

- Infections and Infestations (6 patients in the A+ET arm versus 17 in the ET only arm), of which
    - 6 of the infections, 3 in each arm, were COVID-19 related
- Injury, Poisoning, and Procedural complications (6 in the A+ET arm versus 4 in the ET only arm)
- Cardiac Disorders (5 in the A+ET arm versus 2 in the ET only arm), and
- Neoplasms Benign, Malignant, and Unspecified (5 in the A+ET arm versus 4 in the ET only arm), of which
    - 1 myelodysplastic syndrome event in the A+ET arm was reported only as an SAE and not captured as an IDFS event.

The SAEs included 13 fatal cases, with 9 events in the A+ET arm and 4 events in the ET only arm, which were discussed above.

A review of SAEs in long-term follow-up found no additional safety concerns, no patterns in terms of SAE by SOC, and no notable differences in the types or frequencies of events between arms.

Adverse events of special interest

Neutropenia

A higher incidence of both neutropenia TEAE and neutrophil count decreased was observed in the A+ET arm, with Grade ≥3 neutropenia reported in <20% of patients (Table 54). Patients in the A+ET arm experienced their first neutropenia Grade ≥3 event within a median 1 month after the start of study treatment, with a median event duration of approximately 2 weeks.

Grade ≥3 neutropenia events were not associated with infections. Grade ≥3 neutropenia occurred early on treatment with the majority of dose omissions and reductions occurring within the first 2 and 6 months on study. The events were well managed with dose modifications, per protocol guidance.

Table 54. Summary of Treatment-Emergent Neutropenia Events and Laboratory Neutrophil Counts (April 2021 cutoff)

n (%)	Arm A Abemaciclib + ET N=2791	Arm B ET N=2800
TEAE *Neutropenia*		
Any Grade	1278 (45.8)	157 (5.6)
Grade 3	527 (18.9)	19 (0.7)
Grade 4	19 (0.7)	4 (0.1)
TEAE Febrile Neutropenia		
Grade ≥3	8 (0.3)	0
SAE *Neutropenia*	3 (0.1)	1 (0.0)
SAE Febrile Neutropenia	5 (0.2)	0
Laboratory Neutrophil Count Decreased	Nx = 2722	Nx = 2696
Any Grade	2286 (84.0)	607 (22.5)
Grade 3	502 (18.4)	43 (1.6)
Grade 4	19 (0.7)	7 (0.3)
TEAE *Neutropenia* Leading to…		
All Treatment Discontinuation	1 (0.0)	0 (0.0)
Abemaciclib or All Treatment Discontinuation	22 (0.8)	
Abemaciclib Dose Omissions	435 (15.6)	NA
Abemaciclib Dose Reductions	223 (8.0)	NA

Abbreviations: ET = endocrine therapy; N = number of patients in the safety population; n = number of patients within category; Nx = number of patients with nonmissing baseline and postbaseline results for neutrophil count laboratory assessment; SAE = serious adverse event; TEAE = treatment-emergent adverse event; OS = overall survival.

Data cutoff: 01 April 2021.

The data from monarchE does not give raise to any new issues concerning this previously known risk.

Infections

As of the OS IA1 data cutoff (01 April 2021), the rate of any grade infections was higher in the A+ET arm (51.2%) compared to the ET only arm (39.2%). Most infections were low grade (Grade ≤2). The overall rate of Grade ≥3 or serious infections was 5.6% in the A+ET arm and 3.0% in the ET only arm. Discontinuations of study treatment due to infections were low, with 26 patients (0.9%) in the A+ET

arm and 6 patients (0.2%) in the ET only arm. Influenza was the most frequently reported cause of abemaciclib or all study treatment discontinuation in the A+ET arm.

As of the OS IA1 data cutoff (01 April 2021), a total of 144 patients reported an infection related to Covid-19 or had a positive Covid-19/SARS-CoV-2 test. The majority of AEs were Grade 1 or 2 with a numerically higher incidence of events in the A+ET arm (95 versus 49).

Treatment-emergent SAEs of Covid-19 infection were reported in 15 patients in the A+ET arm and 3 patients in the ET only arm. In addition, 3 SAEs of Covid-19 in each arm were reported in the follow-up period and do not qualify as treatment-emergent.

Including 1 death in the A+ET arm in long-term follow-up that was not treatment-emergent, there were 4 deaths due to infection in the A+ET arm, all due to COVID-19 or suspected COVID-19, and 5 deaths in the ET only arm, one of which was due to COVID-19 pneumonia.

Table 55. Summary of Treatment-Emergent Infection Events (April 2021 cut-off)

n (%)	Arm A Abemaciclib + ET N=2791	Arm B ET N=2800
TEAE Infection (SOC)[a]		
Any Grade	1429 (51.2)	1102 (39.4)
Grade 3	136 (4.9)	75 (2.7)
Grade 4	16 (0.6)	3 (0.1)
Grade 5[b]	3 (0.1)[b]	5 (0.2)
TEAE Preferred Terms within Infection (SOC)[a], with >5% Any Grade incidence in either arm		
URTI	301 (10.8)	238 (8.5)
UTI	336 (12.0)	211 (7.5)
Nasopharyngitis	259 (9.3)	202 (7.2)
SAE Infection (SOC)[a]	146 (5.2)	80 (2.9)
TEAE Infection (SOC)[a] Leading to…		
All Treatment Discontinuation	9 (0.3)	6 (0.2)
Abemaciclib or All Treatment Discontinuation	26 (0.9)	

Abbreviations: ET = endocrine therapy; N = number of patients in the safety population; n = number of patients within category; OS = overall survival; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.

[a] Includes all reported preferred terms that are part of the Infections and Infestations SOC.

[b] An additional death in Arm A due to COVID-19 is not included, as it was during long-term follow-up and not treatment-emergent.

Data cutoff: 01 April 2021.

Diarrhoea

Diarrhoea is the most frequently reported AE in monarchE.

A higher incidence of diarrhoea (any grade) was observed in the A+ET arm compared to the ET only arm (Table 55).

Most events in Arms A and B were low grade but a higher incidence of Grade ≥3 events was observed in the A+ET arm compared to the ET only arm (Table 55). In the A+ET arm, 1 patient died of unclear intra-abdominal pathology (reported term was 'diarrhoea', as it was the initial presenting feature).

In the A+ET arm, 60% of patients with diarrhoea had 1 or 2 episodes and 40% had 3 or more episodes (Table 55).

The median time to onset for the first diarrhoea event was 8 days in the A+ET arm. Median time to onset of Grade ≥2 and Grade ≥3 diarrhoea events was 26.5 and 47.0 days in the A+ET arm,

respectively. The median duration of Grade ≥2 and Grade ≥3 diarrhoea events was ≤6.0 days in the A+ET arm.

Among patients with at least 1 diarrhoea event in the A+ET arm, 78% received anti-diarrhoeal medication, following protocol guidance. Loperamide was the most common treatment.

Complications associated with diarrhoea included dehydration, Grade ≥3 hypokalaemia, and Grade ≥3 hyponatremia. The association between these events and diarrhoea is defined by a temporal association – occurring 1 or 2 days after the end date of abemaciclib use or concurrently.

In total, 1020 patients had dose modifications due to treatment-emergent diarrhoea in the A+ET arm – 479 had dose reductions and 541 had dose omissions.

In the A+ET arm, 146 patients (5.2%) discontinued abemaciclib or all treatments due to diarrhoea.

There was one fatal event reported as diarrhoea. The patient was an 84-year old woman. She was reported to be an ex-alcohol user, tobacco user, with hypertension and type 2 diabetes mellitus (treated with metformin). The time to onset of the event was 6 months. The differential diagnosis was acute abdomen/abdominal sepsis secondary to the diarrhoea event, due to possible intestinal perforation or mesenteric ischemia. The investigator suggested that the most likely diagnosis was mesenteric ischemia leading to death, and that diarrhoea was the presenting symptom.

In the Early breast cancer population, the overall rate of diarrhoea was lower or similar, respectively, to the rates observed in the two MBC Phase 3 studies. The rate of ≥ Grade 3 diarrhoea was lower in monarchE than in both MBC studies. However, treatment discontinuation due to diarrhoea occurred at a higher rate in monarchE (5.2%) than in the MBC studies (1.8% and 2.9%, respectively).

Table 56. Summary of Characteristics of Treatment-Emergent Diarrhoea Events (April 2021 cutoff)

n (%)	Arm A Abemaciclib + ET N=2791	Arm B ET N=2800
TEAE Diarrhea		
Any Grade	2331 (83.5)	242 (8.6)
Grade 3	218 (7.8)	6 (0.2)
Grade 4	0 (0.0)	0 (0.0)
Grade 5	1 (0.0)	0 (0.0)
SAE Diarrhea	15 (0.5)	0 (0.0)
TEAE Diarrhea Leading to…		
All Treatment Discontinuation	68 (2.4)	0 (0.0)
Abemaciclib or All Treatment Discontinuation	146 (5.2)	
Abemaciclib Dose Omissions	541 (19.4)	NA
Abemaciclib Dose Reductions	479 (17.2)	NA

Abbreviations: ET = endocrine therapy; N = number of patients in the safety population; n = number of patients within category; NA = not applicable; OS = overall survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Data cutoff: 01 April 2021.

Hepatic Events

There was a higher incidence of both ALT increased and AST increased in Arm A (ALT increased: 12.3%; AST increased: 11.8%) versus Arm B (ALT increased: 5.6%; AST increased: 4.9%). The frequencies of Grade ≥3 events of ALT/AST increased were higher in Arm A compared to Arm B, however the overall incidence of Grade ≥3 or serious ALT/AST increased events was low (<3%).

In both arms, treatment discontinuations and dose modifications due to ALT or AST increased were low (<2.5%).

In Arm A, a total of 11 patients developed elevation in AST and/or ALT >3X ULN with TBILI >2X ULN per central laboratory. Of these, 2 were new cases since the Final IDFS analysis. In arm B, two patients experienced these elevations.

As elevations in ALT may be indicative of liver injury, a detailed analysis of significant increases based on central laboratory values was conducted. At OS IA1, there were no cases of drug induced liver injury per MAH assessment.

Venous Thromboembolic Events (VTEs)

The composite term *'VTEs'* includes pulmonary embolism (*PE*) and deep vein thrombosis (*DVT*). The PTs included in the composite term are shown in Table 57.

Any grade *VTE* events were reported for 71 (2.5%) patients in the A+ET arm and 17 (0.6%) in the ET only arm, with notable imbalance of Grade ≥3 events in the treatment arms (Table 57).

Serious adverse events were reported for 34 patients in the A+ET arm (including 19 *PE*) and 8 patients in the ET only arm (including 4 *PE*).

Median time to onset of first *VTE* event was between 5 and 6 months of treatment in both arms with a lot of variability in range.

The known risk factors for *VTE,* such as increasing age and body mass index (BMI), were generally balanced across arms. In the A+ET arm, there was a trend for a higher incidence of *PE* and Grade 3/4 V*TE* with increasing BMI, but no trend observed with increasing age.

The higher incidence of *VTEs* in the A+ET arm was consistent regardless of whether patients received tamoxifen or AI as first background ET. However, there was a trend for increased any grade and Grade ≥3 incidence of *VTE*, including *PE*, in patients who received tamoxifen as first background ET compared to those who received AI as first background ET. This is in line with the experience that tamoxifen is associated with a numerically higher incidence of V*TEs* than AIs.

VTEs were managed with anti-coagulation medication, as per protocol recommendations. In the A+ET arm 14 patients who experienced Grade ≥3 *VTEs* discontinued treatment. This number was 2 in the ET only arm.

Table 57. Summary of Treatment-Emergent Venous Thromboembolic Events Preferred Term by Decreasing Frequency (April 2021 cutoff)

n (%)	Arm A Abemaciclib + ET N=2791	Arm B ET N=2800
TEAE *VTE*		
Any Grade	71 (2.5)	17 (0.6)
Grade 3	32 (1.1)	7 (0.3)
Grade 4	6 (0.2)	0 (0.0)
Grade 5[a]	0 (0.0)	1 (0.0)
SAE *VTE*	34 (1.2)	8 (0.3)
SAE *PE*	19 (0.7)	4 (0.1)
TEAE *VTE* Leading to…		
All Treatment Discontinuation	6 (0.2)	2 (0.1)
Abemaciclib or All Treatment Discontinuation	14 (0.5)	
Abemaciclib Dose Omissions	40 (1.4)	NA
Abemaciclib Dose Reductions	4 (0.1)	NA

Interstitial Lung Disease/Pneumonitis

Over 95.0% of patients in both arms had adjuvant radiotherapy, a risk factor for *ILD/pneumonitis,* prior to enrolment in the study.

The incidence of any grade and Grade ≥3 *ILD/pneumonitis* was higher in the A+ET arm compared to the ET only arm, with the vast majority being single occurrences. The majority of the events were Grade 1, usually asymptomatic, identified by imaging, and did not require any intervention. Serious *ILD/pneumonitis* events occurred in 14 (0.5%) patients and 1 (<0.1%) patient in the A+ET arm and B, respectively. There was 1 fatality due to *ILD/pneumonitis* in the A+ET arm and none in the ET only arm (Table 47).

The median time to onset for the first *ILD/pneumonitis* event was approximately 6 months in the A+ET arm.

Table 58. Summary of Treatment-Emergent ILD/Pneumonitis Events – Safety population (April 2021 cutoff)

n (%)	**Arm A Abemaciclib + ET N=2791**	**Arm B ET N=2800**
TEAE *ILD/Pneumonitis*		
Any Grade	89 (3.2)	37 (1.3)
Grade 3	10 (0.4)	0 (<0.1)
Grade 4	0 (0.0)	0 (0.0)
Grade 5	1 (<0.1)	0 (0.0)
SAE *ILD/Pneumonitis*	14 (0.5)	1 (<0.01)
TEAE *ILD/Pneumonitis* Leading to…		
All Treatment Discontinuation	2 (0.1)	0 (0.0)
Abemaciclib or All Treatment Discontinuation	19 (0.7)	
Abemaciclib Dose Omissions	13 (0.5)	NA
Abemaciclib Dose Reductions	5 (0.2)	NA

Abbreviations: ET = endocrine therapy; ILD = interstitial lung disease; N = number of patients in the safety population; n = number of patients within category; NA = not applicable; OS = overall survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Data cutoff: 01 April 2021.

Adverse Events of Note

In addition to AESIs, the MAH discussed some 'Adverse events of Note'.

Skin and Subcutaneous Disorders

Skin and subcutaneous tissue disorders SOC were observed at a higher level in the A+ET arm (40.7%) compared to the ET only arm (22.0%). The most common events were alopecia, pruritus, rash and *nail disorders* (composite term; Table 59).

Treatment-emergent *severe cutaneous adverse reactions* (SCAR; composite term) were infrequent. Three patients in each arm experienced dermatitis bullous (Grade 1). In the A+ET arm, one patient each experienced erythema multiforme (Grade 2), skin necrosis (Grade 2), and toxic skin eruption (Grade 2); in the ET only arm, one patient experienced, two patients experienced dermatitis exfoliative generalized (Grade 1 and Grade 2, respectively) and toxic epidermal necrolysis (Grade 2). In summary, there were no Grade ≥3 or serious SCARs TEAE reported due to abemaciclib.

'Nail disorders' has been added as ADR in section 4.8 of the SmPC.

Table 59. Adverse Reactions within SOC Skin and subcutaneous disorders of Patients Receiving Abemaciclib Plus ET and ET Alone in monarchE (April 2021 cutoff)

System Organ Class Preferred Term	Arm A Abemaciclib + ET N=2791				Arm B ET N=2800			
	CTCAE Grade, n (%)							
	Any grade	3	4	≥3	Any grade	3	4	≥3
Skin and Subcutaneous Tissue Disorders								
Rash[f]	312 (11.2)	11 (0.4)	0	11 (0.4)	127 (4.5)	0	0	0
Alopecia	313 (11.2)	0	0	0	75 (2.7)	0	0	0
Pruritus	242 (8.7)	2 (<0.1)	0	2 (<0.1)	123 (4.4)	1 (<0.1)	0	1 (<0.1)
Nail disorder[g]	166 (5.9)	0	0	0	28 (1.0)	1 (<0.1)	0	1 (<0.1)

Eye Disorders

TEAE in the Eye disorders SOC was observed at a higher frequency in the A+ET arm (14.9%) compared to the ET only arm (6.3%). Increased lacrimation was reported in 5.5% vs. 0.4%, the majority of events being Grade 1. Cataract was reported in 1.2% vs. 0.6%. Grade ≥3 events of cataract occurred in 9 patients (0.3%) in the A+ET arm and 5 patients (0.2%) in the ET only arm.

Fatigue

Fatigue is considered an important TEAE in the EBC population and can affect quality of life. Fatigue was reported in 40.6% of patients in the A+ET arm and 17.8% of patients in the ET only arm, with Grade 1 fatigue comprising the majority in both arms. Grade 3 fatigue (maximum severity) was infrequent, occurring in 2.9% and 0.1% patients in the A+ET arm and the ET only arm, respectively.

Fatigue was one of the most common reasons for dose modifications of abemaciclib. Most of these dose modifications occurred during the first 3 to 4 months of treatment (see below).

Stomatitis

Stomatitis was reported in 385 patients (13.8%) in the A+ET arm and 151 patients (5.4%) in the ET only arm. In both arms, the majority of patients had Grade 1 stomatitis. Grade 3 stomatitis was infrequent in either arm (0.1% vs 0% in Arms A and B, respectively).

Stomatitis has been added as ADR in section 4.8 of the SmPC.

Laboratory findings

Review of the clinical laboratory results, including shift tables, for monarchE did not reveal any new safety concerns.

Significant relevant findings were as follows:

- Baseline laboratory values were generally within normal limits for most of the laboratory parameters. Shifts from baseline to abnormal levels were most common for haematological parameters.
- Creatinine increased is a known laboratory finding in patients treated with abemaciclib and remained above normal during study treatment and returned to baseline after treatment discontinuation. This was not associated with decreased renal function.
- Grade ≥3 haematological laboratory data, WBC decreased, neutrophil count decreased, anaemia, lymphocyte count decreased, and platelet count decreased were generally consistent with the corresponding reported TEAE.
- Laboratory hypokalaemia, hyponatremia, and hypocalcaemia were reported for more patients in the A+ET arm; however, these were mainly Grade 1 events. The occurrence of Grade ≥2 events were infrequent in both arms.

Data for elevated transaminases have been described above.

Adverse drug reactions for the SmPC

Treatment-emergent adverse events and composite terms that were identified as ADRs in abemaciclib-treated patients in MonarchE are summarised in Table 60.

Table 60. Adverse Reactions of Patients Receiving Abemaciclib Plus ET and ET Alone in monarchE (April 2021 cut-off)

System Organ Class Preferred Term	Arm A Abemaciclib + ET N=2791				Arm B ET N=2800			
	CTCAE Grade, n (%)							
	Any Grade	3	4	≥3	Any Grade	3	4	≥3
Gastrointestinal Disorders								
Diarrhea[a]	2331 (83.5)	218 (7.8)	0	219 (7.8)	242 (8.6)	6 (0.2)	0	6 (0.2)
Nausea	824 (29.5)	14 (0.5)	0	14 (0.5)	252 (9.0)	2 (<0.1)	0	2 (<0.1)
Vomiting	491 (17.6)	15 (0.5)	0	15 (0.5)	130 (4.6)	3 (0.1)	0	3 (0.1)
Stomatitis[b]	385 (13.8)	4 (0.1)	0	4 (0.1)	151 (5.4)	0	0	0
Dyspepsia	219 (7.8)	0	0	0	76 (2.7)	0	0	0
Infections and Infestations								
Infections (SOC)[c,d]	1429 (51.2)	136 (4.9)	16 (0.6)	155 (5.6)	1102 (39.4)	75 (2.7)	3 (0.1)	83 (3.0)
Blood and Lymphatic Disorders								
Neutropenia	1278 (45.8)	527 (18.9)	19 (0.7)	546 (19.6)	157 (5.6)	19 (0.7)	4 (0.1)	23 (0.8)
Leukopenia	1049 (37.6)	313 (11.2)	4 (0.1)	317 (11.4)	186 (6.6)	11 (0.4)	0	11 (0.4)
Anemia	681 (24.4)	56 (2.0)	1 (<0.1)	57 (2.0)	104 (3.7)	9 (0.3)	1 (<0.1)	10 (0.4)
Lymphopenia	395 (14.2)	148 (5.3)	3 (0.1)	151 (5.4)	96 (3.4)	13 (0.5)	0	13 (0.5)
Thrombocytopenia	373 (13.4)	28 (1.0)	8 (0.3)	36 (1.3)	52 (1.9)	2 (<0.1)	2 (<0.1)	4 (0.1)
General Disorders and Administration Site Conditions								
Fatigue	1133 (40.6)	80 (2.9)	0	80 (2.9)	499 (17.8)	4 (0.1)	0	4 (0.1)
Nervous System Disorders								
Headache	546 (19.6)	8 (0.3)	0	8 (0.3)	421 (15.0)	5 (0.2)	0	5 (0.2)
Dizziness	304 (10.9)	4 (0.1)	0	4 (0.1)	188 (6.7)	1 (<0.1)	0	1 (<0.1)
Dysgeusia[e]	152 (5.4)	0	0	0	13 (0.5)	0	0	0
Metabolism and Nutrition Disorders								
Decreased appetite	329 (11.8)	16 (0.6)	0	16 (0.6)	68 (2.4)	2 (<0.1)	0	2 (<0.1)
Investigations								
ALT increased	343 (12.3)	72 (2.6)	5 (0.2)	77 (2.8)	157 (5.6)	19 (0.7)	0	19 (0.7)
AST increased	330 (11.8)	49 (1.8)	3 (0.1)	52 (1.9)	137 (4.9)	15 (0.5)	0	15 (0.5)
Skin and Subcutaneous Tissue Disorders								
Rash[f]	312 (11.2)	11 (0.4)	0	11 (0.4)	127 (4.5)	0	0	0
Alopecia	313 (11.2)	0	0	0	75 (2.7)	0	0	0
Pruritus	242 (8.7)	2 (<0.1)	0	2 (<0.1)	123 (4.4)	1 (<0.1)	0	1 (<0.1)
Nail disorder[g]	166 (5.9)	0	0	0	28 (1.0)	1 (<0.1)	0	1 (<0.1)
Eye Disorders								
Lacrimation increased	154 (5.5)	2 (<0.1)	0	2 (<0.1)	10 (0.4)	0	0	0
Composite Terms[h]								
ILD/pneumonitis[i,j]	89 (3.2)	10 (0.4)	0	11 (0.4)	37 (1.3)	1 (<0.1)	0	1 (<0.1)
VTE[k,l]	71 (2.5)	32 (1.1)	6 (0.2)	38 (1.4)	17 (0.6)	7 (0.3)	0	8 (0.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ET = endocrine therapy; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the safety population; n = number of patients per category; OS = overall survival; PT = Preferred Term; SMQ = Standardized MedDRA Query; SOC = System Organ Class; VTE = venous thromboembolic event.

a Includes 1 Grade 5 event in Arm A.

b Includes mouth ulceration, mucosal inflammation, oropharyngeal pain, and stomatitis.

c Includes all reported PTs that are part of the Infections and Infestations SOC. Most common infections (>5%) include upper respiratory tract infection, urinary tract infection, and nasopharyngitis.

d Includes 8 Grade 5 events, 3 in Arm A and 5 in Arm B.

e Includes dysgeusia and taste disorder.

f Includes exfoliative rash, mucocutaneous rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash popular, rash papulosquamous, rash pruritic, rash vesicular, and vulvovaginal rash.

g Includes nail disorder, onychoclasis, onycholysis, onychomadesis, nail ridging, nail discoloration, nail pigmentation, nail bed inflammation, nail dystrophy, nail bed disorder, nail toxicity, and onychalgia.

h Composite terms are defined as a grouping of terms from one or more PTs or SOC that are related to a defined medical condition or area of interest.

i *ILD/pneumonitis* events were defined by SMQ of "interstitial lung disease" as indicated in Section 5.2.1.4.6 and included pneumonitis, radiation pneumonitis, interstitial lung disease, pulmonary fibrosis, lung capacity, organizing pneumonia, radiation fibrosis (lung), pulmonary granuloma, sarcoidosis.

j Includes 1 Grade 5 event in Arm A.

k *VTEs* were defined as indicated in Section 5.2.1.4.5 and included deep vein thrombosis, device related thrombosis, jugular vein thrombosis, cerebral venous thrombosis, subclavian vein thrombosis, catheter site thrombosis, portal vein thrombosis, venous thromobosis limb, hepatic vein thrombosis, jugular vein occlusion, ovarian vein thrombosis, pulmonary embolism, and embolism.

l Includes 1 Grade 5 event in Arm B.

MedDRA Version 24.0; CTCAE Version 4.

Data cutoff: 01 April 2021.

Safety in special populations

TEAEs by age

The median age of the overall population was 51.0 years.

Patients were analysed by years of age, <65 years (younger) and ≥65 years (elderly) for TEAEs and laboratory toxicities.

The following TEAEs (any grade) were >5.0% higher in elderly patients compared to younger patients:

- fatigue
- anaemia
- thrombocytopenia
- decreased appetite
- blood creatinine increased and
- alopecia.

while the following were more common in the younger patient group

- abdominal pain
- headache and
- hot flush.

The overall incidence of any grade TEAEs was similar in both arms across age subgroups; however, elderly patients had approximately 5% higher incidence of Grade ≥3 TEAEs as compared to younger patients in both arms.

Thus, there was a trend for a higher incidence in older patients compared to younger patients (≥65 years versus <65 years) for frequently occurring Grade ≥3 TEAEs such as diarrhoea and fatigue.

Furthermore, in the A+ET arm, there was a trend toward numerically higher incidences of TE-SAEs, fatal TEAEs, and TEAEs leading to discontinuation in elderly patients compared to younger patients.

TEAEs by race

There was a higher incidence of any grade and Grade ≥3 laboratory haematological toxicities in Asian compared to White patients. Grade ≥3 neutropenia and grade ≥3 elevated ALT/AST were higher in Asian compared to White patients.

In general, certain TEAEs were reported at a higher incidence in White patients compared to Asian patients including any grade fatigue, GI TEAEs (such as nausea and vomiting of any grade, and Grade ≥3 diarrhoea).

Any grade ILD/pneumonitis in the A+ET arm was higher in the Asian population compared to the White population although Grade ≥3 incidence was consistent across races.

A similar trend to that observed with race was also observed in the by-region analysis (North America and Europe versus Asia vs Other).

TEAEs by gender

A total of 36 men were enrolled into the study and treated (21 in the A+ET arm and 15 in the ET only arm). Four patients in the A+ET arm have completed the 2-year on-study treatment period, and a total of 29 male patients across the study are still on treatment.

The overall incidence of all grade TEAEs, Grade ≥3 and SAEs in men is comparable to the overall study population. No male patient died or discontinued study treatment due to a TEAE. The majority of male

patients experienced at least 1 TEAE, with Grade ≥3 events observed among 6 patients in the A+ET arm and 2 patients in the ET only arm.

Four of the 36 patients had SAEs, 3 in the A+ET arm (colorectal carcinoma, pneumonitis, pulmonary embolism) and 1 in the ET only arm (deep vein thrombosis) (numbers from the March 2020 cutoff).

Use in Pregnancy and Lactation

In the A+ET arm of the monarchE study, exposure in pregnancy was reported for one patient after being in study for approximately 1 year and 24 days. The patient discontinued study treatment on the day of event detection. Gestational age at the last abemaciclib exposure was 14 weeks. The patient had a successful delivery at gestational age of 39 weeks. No congenital or chromosomal abnormalities were detected. Grade 1 fatigue was the only other TEAE reported in this patient during the pregnancy period.

Safety related to drug-drug interactions and other interactions

The known DDI information for abemaciclib is reflected in the current labelling for abemaciclib. No DDIs have been observed between abemaciclib and standard adjuvant ET such as anastrozole, letrozole, exemestane, or tamoxifen.

Discontinuation due to adverse events

Discontinuations

In the A+ET arm, a total of 515 patients (18.5%) discontinued abemaciclib or abemaciclib and ET due to AEs. Most of the subjects who discontinued all study treatment (181 patients) continued their ET as post-discontinuation therapy.

The 3 most common reasons for discontinuations were: diarrhoea (5.3%), fatigue (2.0%), and neutropenia (0.9%). These 3 most common AEs accounted for nearly half (44%) of all discontinuations. The majority of discontinuations due to diarrhoea and fatigue occurring for low-grade (Grade ≤2) events. The reasons for discontinuation reported for 4 or more patients in the A+ET arm are shown in Table 61.

The highest number of discontinuations due to any AE in the A+ET arm occurred during the first month of treatment, and the frequency of discontinuations diminished over time. The majority of discontinuations, including those due to diarrhoea, fatigue, and neutropenia, occurred within first 6 months of treatment. Discontinuations were rare after 12 months of treatment.

More than half of discontinuations due to TEAEs occurred without a prior dose reduction.

Table 61. Adverse Events Reported as Reason for Abemaciclib or All Treatment Discontinuation by SOC Greater than or Equal 0.1% Decreasing Frequency in the A+ET arm (01 Apr 2021 data cut-off)

Preferred Term	LY2835219-150mg+EDT (N=2791) n (%)
Subjects Discontinued Abemaciclib or All Treatments due to AE	515 (18.5)
Diarrhoea	147 (5.3)
Fatigue	56 (2.0)
Neutropenia	25 (0.9)
Abdominal pain	20 (0.7)
Alanine aminotransferase increased	16 (0.6)
Pneumonitis	13 (0.5)
Nausea	11 (0.4)
Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Vomiting	7 (0.3)
Deep vein thrombosis	7 (0.3)
Aspartate aminotransferase increased	6 (0.2)
Gamma-glutamyltransferase increased	5 (0.2)
Rash	5 (0.2)
Depression	5 (0.2)
Anaemia	4 (0.1)
Pulmonary embolism	4 (0.1)

[c, d, e, f] Composite terms are defined as a grouping of terms from one or more PTs or SOC that are related to a defined medical condition or area of interest. For definitions of composite terms, see section Adverse Events of Special Interest

Dose modifications

Table 62 summarises dose modifications for patients in the safety population, which include dose omissions and reductions.

Abemaciclib dose modifications due to AEs were very common, with 1212 patients (43.4%) with at least 1 dose reduction and 1721 patients (61.7%) with at least 1 dose omission. A total of 387 patients (13.9 %) needed 2 dose reductions due to AEs. The most frequent reason for dose modifications of abemaciclib in monarchE was AEs, specifically diarrhoea, fatigue, and haematological toxicities: neutropenia and leukopenia .

The majority of patients could continue treatment with the reduced dose. Thus, in general treatment-emergent AEs (TEAEs) related to abemaciclib could be managed with appropriate dose modifications allowing most patients to remain on treatment. Most dose reductions occurred early on during study treatment.

Also, most dose omissions due to AEs occurred early on during study treatment. The median duration of the abemaciclib dose omissions represented 4.9% of the overall study treatment duration per patient.

The most common AEs leading to dose reduction or dose omission were diarrhoea, neutropenia, fatigue and leukopenia (Table 62).

Table 62. Dose Modifications for Abemaciclib in the A+ET arm (01 Apr 2021 data cut-off)

Parameter	LY2835219-150mg+EDT (N=2791) LY2835219 n (%)
Patients with at least one Dose Adjustment n(%)	2014(72.2)
Number of Patients with Dose Reduction	1217(43.6)
Patients with 1 dose reduction	829(29.7)
Patients with 2 dose reductions	387(13.9)
Patients with >= 3 dose reductions	1(0.0)
Reasons leading to dose reduction	
Adverse Events*	1212(43.4)
Diarrhoea	482(17.3)
Neutropenia	226(8.1)
Fatigue	125(4.5)
Leukopenia	99(3.5)
PROTOCOL	3(0.1)
Number of Patients with Dose Omission	1908(68.4)
Patients with 1 dose Omission	805(28.8)
Patients with 2 dose Omissions	536(19.2)
Patients with >= 3 dose Omissions	567(20.3)
Reasons leading to Dose Omissions	
Adverse Events*	1721(61.7)
Diarrhoea	543(19.5)
Neutropenia	440(15.8)
Leukopenia	195(7.0)
Fatigue	140(5.0)
PRE-PLANNED SURGERY	363(13.0)
SCHEDULING CONFLICT	114(4.1)
TREATMENT AVAILABILITY	26(0.9)
Number of Patients with Dose Increase	11(0.4)

Abbreviations: N = number of subjects in Safety Population; n = number of subjects in the specified category.
* AE preferred terms reported in more than 3% of patients.

Post marketing experience

Cumulatively, as of 27 March 2020, approximately 328 healthy volunteers and 6172 patients have received abemaciclib in clinical trials.

Cumulatively, as of 31 July 2020, it is estimated that approximately 34800 patients have received abemaciclib worldwide from post-marketing sources.

2.5.1. Discussion on clinical safety

The data described in the initial application reflect the results of the pre-planned interim analysis 2 (IA2) of study monarchE, with the data cut-off date of 16 March 2020.

At the interim analysis, the median duration of treatment with abemaciclib in monarchE was 14 months. During the procedure, the MAH provided additional safety data, with a cut-off date of 8 July 2020 (final IDFS analysis) and 01 April 2021 (OS IA1 analysis), respectively. The median follow-up at OS IA1 was 27 months. The updated data were overall in agreement with the originally submitted data.

Adverse events

Most TEAEs were reported within the SOCs gastrointestinal disorders, Blood and lymphatic disorders, General disorders and administration site conditions and Infections and infestations.

The far most commonly reported TEAE was diarrhoea, observed in 83% of the patients treated with abemaciclib. Of these, 40% had three or more events. Most of the events were of Grade 1-2. Grade ≥3

diarrhoea occurred in about 8% of patients. Diarrhoea generally occurred early during treatment and was relatively often associated with abdominal pain. The rate of diarrhoea in the EBC population was not greater than in the MBC population, but a larger proportion of EBC patients discontinued treatment due to diarrhoea.

The other most common TEAEs by PT (reported in ≥ 20% of the patients in the A+ET arm) were neutropenia, fatigue, leukopenia, abdominal pain, nausea, anaemia, and arthralgia. Arthralgia was the only one of these that was observed to a similar or larger extent in the ET only arm than in the A+ET arm.

The most common Grade ≥3 TEAEs (>2.0%) in the A+ET arm included neutropenia, leukopenia, diarrhoea, lymphopenia, and fatigue. Neutropenia Grade ≥3 was reported in 20% of patients in the abemaciclib treatment arm. Grade ≥3 neutropenia events were not clearly associated with infections and were managed with dose modifications. There was, however, a clear imbalance in AEs related to Covid-19 infection between treatment arms. Such events were reported for 95 subjects in the A+ET arm and 49 subjects in the ET only arm. Grade ≥3 Covid-19 related AEs were reported in 16 and 4 patients in the A+ET arm and the ET only arm, respectively.

Any grade VTE events (pulmonary embolism or deep vein thrombosis) were reported for 63 (2.3%) patients in the A+ET arm and 14 (0.5%) in the ET only arm, with notable imbalance of Grade ≥3 events in the treatment arms; 33 (1.2%) patients in the A+ET arm and 5 (0.2%) patients in the ET only arm. Serious adverse events were reported for half of the patients experiencing a VTE in either arm. VTEs were managed with anti-coagulation medication and in the A+ET arm, 27% of the patients who experienced Grade ≥3 VTEs discontinued treatment. The data from monarchE do not give raise to any new issues concerning this previously known risk.

New ADRs identified for inclusion in section 4.8 of the SmPC include headache, dyspepsia, stomatitis and nail disorder. The AEs cough and constipation occurred more frequently in the A+ET arm compared to the ET only arm. These AEs were observed also in the MBC studies Monarch 2 and Monarch 3, but there were no notable differences between treatment arms. The differences between treatment arms for these reactions in monarchE was smaller than for many other of the reactions included in the ADR table. Most events were of Grade 1 or 2. These reactions are therefore not considered sufficiently 'clinically significant' to be listed as ADRs.

Safety in special populations

Subgroup analysis of efficacy data in the elderly subgroup indicated a trend towards lower efficacy in the abemaciclib-treated patients than in ET-only treated patients. This raises concern about whether a lower tolerability to abemaciclib in elderly patients might have led to a higher rate of discontinuation not only of abemaciclib but also of ET in this subgroup, and thereby a loss of chance as compared with patients treated with ET only.

The differences in the findings in the TEAEs by race do not change the overall risk-benefit in these subgroups and are generally consistent with prior findings of abemaciclib in combination with ET in MBC studies.

The observed safety profile in the 36 men enrolled into the study and treated, is comparable to the overall study population.

Serious adverse events (SAEs) and deaths

The most frequent cause of SAEs in the A+ET arm by SOC were infections and infestations, followed by gastrointestinal disorders. The most common SAEs by PTs in the A+ET arm were reported under the composite term 'venous thromboembolic events' (VTEs; including pulmonary embolism, PE, and deep

vein thrombosis, DVT) and pneumonia. The pattern of SAEs in EBC does not give raise to new concerns as compared with MBC.

Treatment-emergent SAEs of Covid-19 infection were reported in 15 patients in the A+ET arm and 3 patients in the ET only arm. In addition, 3 SAEs of Covid-19 in each arm were reported in the follow-up period and do not qualify as treatment-emergent. Thus, there was an imbalance in Covid-19 related SAEs between treatment arms.

Deaths due to AEs

There was an apparent imbalance in deaths due to AEs between the A+ET arm (24 cases) and the ET only arm (14 cases). The main differences between the treatment arms were, in the A+ET arm:

- deaths due to Cardiac disorders (5 in the A+ET arm, zero in the ET only arm)
- death due to Nervous system disorders (2 in the A+ET arm and zero in the ET only arm)
- death related to Covid-19 or suspected Covid-19 (4 in the A+ET arm and 1 in the ET only arm),

and in the ET only arm:

- death due to Infections/infestations (4 patients in the ET only arm and zero in the A+ET arm; excluding deaths related to Covid-19).

Regarding infections it is noted that the rate of *serious* (non-fatal) infections was greater in the A+ET arm than in the ET only arm. The higher rate of death due to infection in the ET only arm therefore appears to be a chance finding. It is also noted that there were more patients (4 patients) who died of Covid-19 or suspected Covid-19 related pneumonia in the A+ET arm than in the ET only arm (1 patient). Two of the patients who died of Covid-19 or suspected Covid-19 in the A+ET arm had relevant risk factors for severe Covid-19 disease.

There were two deaths reported within SOC gastrointestinal disorders in the Abemaciclib + ET arm, one case due to mesenteric artery thrombosis, and the other case reported due to diarrhoea but could not be ruled out that this was a symptom of mesenteric ischemia.

Regarding the five deaths due to cardiac disorders, the MAH argues that all patients had other risk factors for such events. A more in-depth review of cardiac disorders reported in association with abemaciclib treatment in Phase 3 trials and post-marketing reports, submitted during the procedure did not indicate discernible pattern among the cardiac events reported on abemaciclib treatment. The most common SAE within the SOC cardiac disorders was atrial fibrillation, which does not indicate a common etiology with the cardiac deaths reported in monarchE.

In summary, there appears to be no particular temporal pattern and, except for deaths due to COVID-19, no pattern or common underlying pathophysiological cause of death in either treatment arm. None of the deaths were considered related to study treatment, with the possible exception of a single case reported as diarrhoea, where the cause of death was not entirely clear.

Discontinuations due to adverse events

The discontinuation rate due to AEs was overall greater in the EBC population than what has been previously observed in the MBC populations.

Many discontinuations occurred relatively early during treatment and a fairly large proportion of discontinuations were not preceded by dose reductions. As the MAH suggests, this could be due to a lower acceptance of AEs affecting daily life in a younger, often actively working patient population. The most common reasons for discontinuations of abemaciclib were diarrhoea, fatigue, neutropenia and leukopenia, with the majority of discontinuations due to diarrhoea and fatigue occurring for low-grade

(Grade ≤2) events. Of note, the majority of patients who discontinued abemaciclib early stayed on the 2-year treatment period receiving ET.

The most frequent reasons for discontinuation of abemaciclib, diarrhoea and fatigue, were the same across subgroups, also in the groups with a clearly higher rate of discontinuations due to AEs, i.e. patients ≥65 years of age, postmenopausal status (which could be due to co-variation with age ≥65) and with ECOG status ≥1.

Across all subgroups most of the discontinuations were due to low-grade AEs and occurred during the first months of treatment, with slightly higher rates of discontinuations due to low-grade AEs in the ≥ 65 years and ECOG ≥ 1 subgroups. Discontinuations due to fatigue were more common in patients ≥65 years than in patients < 65 years. A similar pattern was observed for patients with ECOG status ≥1 compared with ECOG status 0. Thus, the data indicate a lower tolerability threshold in these groups.

Additional adverse drug reactions for the SmPC, section 4.8

The MAH used statistical analysis and medical judgment for the assessment of adverse drug reactions (ADRs). Events that met the initial screening criteria or were considered medically informative and clinically significant were designated as an ADR for abemaciclib plus ET in EBC.

Newly determined ADRs not currently identified for any previously approved indication of abemaciclib are headache, dyspepsia, and nail disorder. In addition, stomatitis is not previously included in the ADR table in the EU SmPC but is included in the approved US drug label for MBC.

The majority of these newly determined ADRs were Grade 1/2 and the MAH does not consider them to have an impact on tolerability.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of abemaciclib + ET in the proposed indication does not give raise to qualitatively new safety concerns as compared with the MBC population.

Thus, the AE profile of abemaciclib + ET in the proposed indication appears overall similar to that previously established in the EBC population. Also, the pattern and frequencies of AEs of special interest (such as diarrhoea, neutropenia and VTE) does not give raise to any new concerns as compared with the MBC population. However, the impact and acceptability of adverse effects differs between an adjuvant setting, where most patients no longer have cancer at baseline, and in the setting of treatment of an advanced malignancy. Overall, the safety profile of abemaciclib is non-trivial, as reflected by an increase in thromboembolic events, pneumonia and overall on-treatment deaths.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 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 1.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Table 63. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Reproductive and developmental toxicity
Missing information	Exposure and safety in patients with severe renal impairment

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 64. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Sections 4.1 and 4.6 • Recommendations for pre-/perimenopausal women who are administered with abemaciclib in combination with endocrine therapy are included in SmPC Section 4.1. • Recommendation for women of childbearing potential are in SmPC Section 4.6.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy and Breastfeeding Maternal follow-up form **Additional pharmacovigilance activities:** None
Exposure and safety in patients with severe renal impairment *(Missing information)*	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2 • Recommendations and information for administering abemaciclib in patients with severe renal impairment are in SmPC Sections 4.2 and 5.2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Abbreviation: SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

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

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:

"The proposed text modifications to the package leaflet resulting from the addition of this new indication are minor and do not include text that is significantly different from that already user tested. Overall, the structure and design of the revised Verzenios Package Leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability. Therefore, the MAH does not consider necessary to conduct further consultation with target patient groups further to that performed for the initial MAA."

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant is seeking an extension of indication as follows:

Verzenios in combination with endocrine therapy (ET) is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section 5.1).

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

In section 5.1 of the SmPC the high risk of recurrence is defined as: either ≥ 4 positive axillary lymph nodes (pALN), or 1-3 pALN and at least one of the following criteria: tumour size ≥ 5 cm, histological grade 3.

3.1.2. Available therapies and unmet medical need

Treatment decisions are often based on multiple factors such as demography (for example, age), clinicopathological risk factors, and sensitivity to available systemic therapies (for example, HR and HER2 status) (ESMO – Cardoso et al. 2019). Patients at higher risk of recurrence will often receive more aggressive treatment in the form of chemotherapy (either neoadjuvant or adjuvant), surgery, and/or radiotherapy, constituting the patient's primary treatment (ESMO – Cardoso et al. 2019). Following primary treatment, patients with HR+ disease will receive ET for at least 5 years.

Patients with lymph node-positive disease are most often candidates for chemotherapy. Standard adjuvant chemotherapy includes anthracycline and/or taxane-based regimen. Adjuvant ET is indicated in all patients with detectable ER expression (defined as ≥1% of invasive cancer cells) irrespective of the use of chemotherapy, for at least 5 years (ESMO - Senkus et al. 2015; Saint Gallen International

Expert Consensus - Coates et al. 2015; National Comprehensive Cancer Network [NCCN] Version 6.2020). The choice of endocrine agent (tamoxifen and/or 1 of the 3 selective aromatase inhibitors [AIs]: anastrozole, letrozole, or exemestane) is primarily determined by the patient's menopausal status. All AIs have shown similar antitumour efficacy and toxicity profiles in randomised studies in the adjuvant and pre-operative setting.

Patients with HR+, HER2- early breast cancer are candidates for treatment with the goal to prevent recurrence and death. With standard therapies alone, up to 20% of patients with HR+, HER2- disease will experience disease recurrence in the first 10 years, often with distant metastasis, at which time the disease is incurable (EBCTCG 2015; Sparano et al. 2017). Providing new treatment options to complement ET addresses a critical unmet medical need for this population of patients with early breast cancer at high risk of recurrence.

3.1.3. Main clinical studies

The pivotal trial for this application is monarchE, a Phase 3, global, randomized, open label study of abemaciclib combined with standard adjuvant ET (A+ET) versus standard adjuvant ET alone in patients with high-risk, node positive, early stage, HR+, HER2-, breast cancer. The study design is presented in Figure 3.

The primary objective was to evaluate the efficacy, in terms of IDFS.

Efficacy endpoints in the hierarchical test structure included IDFS in the ITT population (primary analysis population), in the ITT Ki-67 High population, in the Cohort 1 Ki-67 High population and OS of the ITT population, in the listed order. IDFS in the Cohort 2 population, with lower risk than Cohort 1 based on 1-3 positive axillary lymph nodes, but classified as Ki-67 High, was an exploratory analysis.

In alignment with the CHMP guideline on evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5), and scientific advice prior to initiation of the monarchE study (EMA/CHMP/SAWP/87150/20177), the primary endpoint, IDFS, is an acceptable mechanism to evaluate efficacy for the evaluation of benefit/risk.

3.2. Favourable effects

5637 patients were randomized and a total of 323 IDFS events were observed in the ITT population at the time of second IDFS pre-planned interim analysis.

The primary endpoint of IDFS was met at the second efficacy interim analysis, demonstrating a statistically significant improvement (two-sided p=.0096) in IDFS with the A+ET arm compared to the ET only arm, HR=0.747 (95% CI: 0.598, 0.932).

At the final IDFS analysis, with a median follow-up time of 19.1 months, statistical significance was also reached for Ki-67 High patients in the ITT population and in Cohort 1.

Data with longer follow-up (corresponding to the first interim analysis of OS), with a median follow-up of 27.7 months in Cohort 1 population have been presented. At this data cut-off, 73.3% of the patients had completed 2-years on study treatment and 17.4% discontinued early from the study treatment period. 8.5% of the patients were still on study treatment. Median follow-up in patients off treatment were 6.0 months for Cohort 1.

A total of 536 IDFS events were observed in the Cohort 1 population at the first interim analysis for OS, including 218 (8.5%) events in the A+ET arm and 318 (12.4%) events in the ET only arm (HR=0.680, 95% CI: 0.572, 0.808).

445 DRFS events were observed in the Cohort 1 population at this time. This included 179 (7.0%) events in the A+ET arm and 266 (10.4%) events in the ET only arm. The HR estimate was 0.669 (0.554, 0.809).

3.3. Uncertainties and limitations about favourable effects

Even though data with longer follow-up have been provided, the follow-up time is still relatively limited given the known relapse pattern of HR+ breast cancer, precluding exact estimates of the clinical efficacy endpoints in a longer-term perspective.

Overall survival data at the first interim analysis of OS are still immature. The HR estimate for OS was 1.044 (95% CI 0.778, 1.401) comparing patients from Cohort 1 treated with abemaciclib + ET to patients treated with ET. This indicates uncertainty of the size of the clinical benefit on OS of adjuvant abemaciclib added to ET for patients with high-risk early breast cancer (see discussion on Clinical Efficacy and B/R).

Given the observed absolute difference in DRFS of 3.4% between the treatment arms in Cohort 1, in favour of abemaciclib, the OS results may at least be expected not to be detrimental for the addition of abemaciclib to standard ET for the high-risk population defined in Cohort 1.

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

Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy and safety of Verzenios in combination with endocrine therapy for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence, the MAH should submit a 5-year follow-up of the monarchE study.

3.4. Unfavourable effects

The safety population from study monarchE included 2791 patients treated with abemaciclib + endocrine therapy (the A+ET arm) and 2800 patients treated with endocrine therapy alone (the ET only arm).

Among patients in A+ET arm, 72% had at least 1 dose modification (dose omission or dose reduction). Dose omissions were made in 68% of patients, with 20% of patients having ≥3 dose omissions. Approximately 44% of patients in the A+ET arm had at least one dose reduction, and 14% had two dose reductions. Almost all dose modifications were due to AEs, the most common reasons were diarrhoea, neutropenia, fatigue and leukopenia.

In the A+ET arm, 18.5% of patients discontinued abemaciclib or abemaciclib and ET due to AEs, versus 1.1% in the ET only arm. The most common reasons for discontinuation in the A+ET arm were diarrhoea (5.3%), fatigue (2.0%), and neutropenia (0.9%), with the majority of discontinuations due to diarrhoea and fatigue occurring for low-grade (Grade ≤2) events.

The discontinuation rate is greater than what has been previously observed in the MBC populations. A fairly large proportion of discontinuations were not preceded by dose reductions and occurred relatively early during treatment. This could be due to a lower acceptance of AEs affecting daily life in a younger, often actively working patient population.

The AE profile of abemaciclib + ET in the early breast cancer population appears largely similar to that previously established in the metastatic breast cancer population, with a qualitatively similar pattern of TEAEs or SAEs.

Thus, most TEAEs in the A+ET arm were reported within the SOCs gastrointestinal disorders, Blood and lymphatic disorders, General disorders and administration site conditions and Infections and infestations.

The most common TEAEs by PT in the A+ET arm were diarrhoea (83.5%), neutropenia (45.8%), fatigue (40.6%), leukopenia (37.6%), abdominal pain (35.5%), nausea (29.5%), arthralgia (26.6%), anaemia (24.4%).

The most common Grade ≥3 TEAEs include neutropenia (19.6%), leukopenia (11.4%), diarrhoea (7.8%), lymphopenia (5.4%), fatigue (2.9%).

The most frequent cause of SAEs by SOC were infections and infestations (5.2% versus 2.9% in the ET only arm) followed by gastrointestinal disorders (2.1% versus 0.6% in the ET only arm).

The most common SAEs by PTs in the A+ET arm were

- the composite term 'venous thromboembolic events' (VTEs; including pulmonary embolism, PE, and deep vein thrombosis, DVT; 1.2% in the A+ET arm versus 0.3% in arm B)
- pneumonia (1.0% in the A+ET arm and 0.6% in arm B).

There were more deaths due to AEs in the A+ET arm than in the control arm, during and within 30 days of treatment as well as >30 days after treatment. In total there were 24 deaths (0.86%) due to AEs in the A+ET arm and 14 (0.50%) in the ET only arm. There were 5 deaths due to cardiac events in the A+ ET arm and none in the ET only arm, but there was no clear pattern among the events in the A+ET arm. There were 4 deaths due to Covid-19 or suspected Covid-19 in the A+ET arm versus one Covid-19 related death in the ET only arm. There appeared to be no common etiology for the reported deaths in the A+ET arm, and the deaths due to AEs were overall not considered treatment-related by the investigator. However, causality may not readily be assessed in the singular cases.

3.5. Uncertainties and limitations about unfavourable effects

Not identified.

3.6. Effects Table

Table 65. Effects Table for Verzenios in combination with ET in the treatment of Early Breast cancer in Cohort 1 (data cut-off: April 2021)

Effect	Short description	Unit	Abemaciclib +ET	ET	Uncertainties / Strength of evidence
IDFS	INV, STEEP criteria	N (%)	218 (8.5)	318 (12.4)	Statistically significant results were obtained in the ITT-population for IDFS at the second interim analysis (HR 0.747 (95% CI 0.598, 0.932) p=0.00957). The Cohort 1 population was not a predefined analysis patient population.
		HR (95% CI)	0.680 (0.572, 0.808)		Median follow- up time was 27.7 months in Cohort 1.
DFS		N (%)	179 (7.0)	266 (10.4)	The presented KM-curves of IDFS and DRFS from the latest DCO do not suggest that the curves would be converging and do not raise any concerns regarding a diminishing efficacy of addition of abemaciclib to ET over time and the presented effect size is of similar range as other approved therapies (i.e., letrozole, neratinib).
		HR (95% CI)	0.669 (0.554, 0.809)		

Effect	Short description	Unit	Abemaciclib +ET	ET	Uncertainties / Strength of evidence
OS					
		N (%)	90 (3.5)	88 (3.4)	
		HR (95% CI)	1.044 (0.778, 1.401)		OS data is immature.

Unfavourable Effects						
Effect	Unit	Treatment		Control		References
		All grades	Grade ≥3	All grades	Grade ≥3	
Diarrhoea	%	83.1	7.8	8.6	0.2	monarchE
Neutropenia	%	45.8	19.6	5.6	0.8	"
Composite term 'ILD/pneumo-nitis'[a]	%	3.2	0.4	1.3	<0.1	"
Composite term 'VTE'[b]	%	2.5	1.4	0.6	0.3	"
Treatment discontinua-tions due to an AE	%	6.5		1.1		"

[a]ILD/Pneumonitis included e.g. the PTs: pneumonitis, radiation pneumonitis, interstitial lung disease, pulmonary fibrosis, organising pneumonia
[b]VTE = venous thrombotic events included PTs under pulmonary embolism and deep vein thrombosis

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study is formally positive. The primary endpoint, IDFS in the ITT population, was positive at the second interim analysis. A clinically relevant and well-recognised high-risk population was identified in the Cohort 1 subpopulation for the addition of abemaciclib to ET (A+ET).

In Cohort 1, the absolute difference in IDFS rate is 3.4% at a median follow-up of 27.7 months, with HRs remaining stable at the different data cut-offs presented and KM-curves maintaining a separating trend for the A+ET arm compared to the ET only arm. The IDFS results in the Cohort 1 population are considered to be clinically relevant, insofar as their magnitude is similar to what has been considered clinically relevant for previous drug approvals for early breast cancer.

Qualitatively, the safety profile for abemaciclib + ET in the early breast cancer population does not give raise to any new concerns compared with previous experience in metastatic breast cancer. The SmPC contains relevant information on the known risks and their management. Nevertheless, the safety profile must be weighed against the expected benefit in the adjuvant setting, where many treated patients might be already cured.

With OS data still immature, the estimated hazard ratio for OS for Cohort 1 was 1.044 (95% CI: (0.778, 1.401)), driven by more deaths reported to be due to AEs in the A+ET arm. However, the overall number of deaths due to AEs is small. In the safety population 0.86% deaths were reported to be due to AEs in the A+ET arm and 0.50% in the ET only arm, and the imbalance could be a chance finding. The imbalance was primarily seen in deaths due to cardiac disorders (5 versus none in the A+ET and ET only arms, respectively) with no common etiology, and death due to Covid-19 (4 versus 1).

Deaths due to other infections were, however, more frequent in the ET only arm (4 vs. 0). Most of the patients had other risk factors for the conditions leading to death.

Importantly, over 90% of the patients are off treatment with abemaciclib and the number of deaths due to AEs is therefore unlikely to increase to any significant degree. Further, it is considered probable that the absolute difference in distant recurrence-free survival observed in Cohort 1 will translate into at least a non-detrimental OS with longer follow-up.

Thus, clinical benefit has been demonstrated in the Cohort 1 population. However, there is a need for further follow-up of overall survival and the temporal pattern of relapse. 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 monarchE study. This has been reflected in the RMP and Annex II.

3.7.2. Balance of benefits and risks

The demonstrated clinical benefit of adding abemaciclib to endocrine therapy in the adjuvant treatment of early breast cancer is sufficient to outweigh the potential risks with abemaciclib treatment in the high-risk population defined by clinicopathological features: ≥ 4 pALN or 1-3 pALN and tumour size ≥ 5 cm or; histological grade 3.

However, there is a need for further follow-up of overall survival and the temporal pattern of relapse. 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 monarchE study. This has been reflected in the RMP and Annex II.

3.7.3. Additional considerations on the benefit-risk balance

A SAG-O meeting was held on 13 January 2022. The majority of the experts supported the notion that clinical benefit has been shown in a population corresponding to Cohort 1 of the pivotal trial.

3.8. Conclusions

The overall B/R of abemaciclib in the applied indication is positive.

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

Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy and safety of Verzenios in combination with endocrine therapy for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence, the MAH should submit a 5-year follow-up of the monarchE study.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 27 out of 28 votes, 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	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication to include Verzenios in combination with endocrine therapy for adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence; as a consequence, section 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, by a majority of 27 out of 28 votes, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

Divergent position to the majority recommendation is appended to this report.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Verzenios-II-0013'

Appendix

1. Divergent position, dated 24 February 2022

DIVERGENT POSITION DATED 24 February 2022

Verzenios EMEA/H/C/004302/II/0013

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the following restricted new indication for Verzenios:

> Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section 5.1).
>
> In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

The reason for divergent opinion was the following:

It is acknowledged that the study is formally positive for IDFS, but the currently available follow-up (median follow-up time 27 months, median follow-up off-treatment 6 months) is not considered of sufficient length for the sought adjuvant treatment, in a setting in which recurrences are expected also beyond 5 years, and in relation to the planned 24-month treatment duration. The submitted follow-up time precludes the demonstration of an increased cure rate as it is unable to exclude a potential rebound effect upon treatment termination.

This limitation in follow-up time is also reflected by a largely immature OS in cohort 1, whose current HR estimate (HR 1.044, 95%CI 0.778, 1.401) is at present unable to support clinical benefit in the target population.

Based on the above, and further in the presence of non-negligible toxicity and in the absence of support from external data from drugs with the same mechanism of action in the same setting, the B/R of Verzenios in the sought indication is currently deemed undetermined.

Armando Genazzani