ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 50 mg film-coated tablets
Verzenios 100 mg film-coated tablets
Verzenios 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Verzenios 50 mg film-coated tablets

Each film-coated tablet contains 50 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 14 mg of lactose monohydrate.

Verzenios 100 mg film-coated tablets

Each film-coated tablet contains 100 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 28 mg of lactose monohydrate.

Verzenios 150 mg film-coated tablets

Each film-coated tablet contains 150 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 42 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Verzenios 50 mg film-coated tablets

Beige, oval tablet of 5.2 x 9.5 mm, debossed with “Lilly” on one side and “50” on the other.

Verzenios 100 mg film-coated tablets

White, oval tablet of 6.6 x 12.0 mm, debossed with “Lilly” on one side and “100” on the other.

Verzenios 150 mg film-coated tablets

Yellow, oval tablet of 7.5 x 13.7 mm, debossed with “Lilly” on one side and “150” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Early breast cancer

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.

Advanced or metastatic breast cancer

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

In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

4.2 Posology and method of administration

Verzenios therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

Posology

The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Please refer to the summary of product characteristics of the endocrine therapy combination partner for the recommended posology.

Duration of treatment

Early breast cancer
Verzenios should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs.

Advanced or metastatic breast cancer
Verzenios should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

If a patient vomits or misses a dose of Verzenios, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Dose adjustments

Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1-7.

Table 1. Dose adjustment recommendations for adverse reactions

	Verzenios dose combination therapy
Recommended dose	150 mg twice daily
First dose adjustment	100 mg twice daily
Second dose adjustment	50 mg twice daily

Table 2. Management recommendations for haematologic toxicities

Complete blood counts should be monitored prior to the start of Verzenios therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated. Before treatment initiation, absolute neutrophil counts (ANC) ≥ 1 500 / mm^3, platelets ≥ 1 00 000 / mm^3, and haemoglobin ≥ 8 g/dL are recommended.

Toxicity[a, b]	**Management recommendations**
Grade 1 or 2	No dose adjustment required.
Grade 3	Suspend dose until toxicity resolves to Grade 2 or less. Dose reduction is not required.
Grade 3, recurrent; or Grade 4	Suspend dose until toxicity resolves to Grade 2 or less. Resume at next lower dose.
Patient requires administration of blood cell growth factors	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade 2 or less. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

[a] NCI Common Terminology Criteria for Adverse Events (CTCAE)
[b] ANC: Grade 1: ANC < LLN – 1 500 / mm^3; Grade 2: ANC 1 000 - < 1 500 / mm^3;
Grade 3: ANC 500 - < 1 000 / mm^3; Grade 4: ANC < 500 / mm^3
LLN = lower limit of normal

Table 3. Management recommendations for diarrhoea

Treatment with antidiarrhoeal agents, such as loperamide, should be started at the first sign of loose stools.

Toxicity [a]	**Management recommendations**
Grade 1	No dose adjustment required.
Grade 2	If toxicity does not resolve within 24 hours to Grade 1 or less, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4 or requires hospitalisation	

[a] NCI CTCAE

Table 4. Management recommendations for increased aminotransferases

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored prior to the start of Verzenios therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

Toxicity[a]	Management recommendations
Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	No dose adjustment required.
Persistent or Recurrent Grade 2, or Grade 3 (> 5.0 - 20.0 x ULN)	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Elevation in AST and/or ALT > 3 x ULN WITH total bilirubin > 2 x ULN, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 (> 20.0 x ULN)	Discontinue abemaciclib.

[a] NCI CTCAE
ULN = upper limit of normal

Table 5. Management recommendations for interstitial lung disease (ILD)/pneumonitis

Toxicity[a]	Management recommendations
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

[a] NCI CTCAE

Table 6. Management recommendations for venous thromboembolic events (VTEs)

Toxicity[a]	Management recommendations
Early breast cancer	
All Grades (1, 2, 3, or 4)	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.
Advanced or metastatic breast cancer	
Grade 1 or 2	No dose modification is required.
Grade 3 or 4	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.

[a] NCI CTCAE

Table 7. Management recommendations for non-haematologic toxicities (excluding diarrhoea, increased aminotransferases, and ILD/pneumonitis and VTEs)

Toxicity [a]	Management recommendations
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4	

[a] NCI CTCAE

CYP3A4 inhibitors
Concomitant use of strong CYP3A4 inhibitors should be avoided. If strong CYP3A4 inhibitors cannot be avoided, the abemaciclib dose should be reduced to 100 mg twice daily.

In patients who have had their dose reduced to 100 mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose should be further reduced to 50 mg twice daily.

In patients who have had their dose reduced to 50 mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose may be continued with close monitoring of signs of toxicity. Alternatively, the abemaciclib dose may be reduced to 50 mg once daily or discontinued.

If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor).

Special populations

Elderly
No dose adjustment is required based on age (see section 5.2).

Renal impairment
No dose adjustments are necessary in patients with mild or moderate renal impairment. There are no data regarding abemaciclib administration in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section 5.2). Abemaciclib should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity.

Hepatic impairment
No dose adjustments are necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, a decrease in dosing frequency to once daily is recommended (see section 5.2).

Paediatric population
The safety and efficacy of abemaciclib in children and adolescents aged less than 18 years has not been established. No data are available.

Method of administration

Verzenios is for oral use.

The dose can be taken with or without food. It should not be taken with grapefruit or grapefruit juice (see section 4.5).

Patients should take the doses at approximately the same times every day.

The tablet should be swallowed whole (patients should not chew, crush, or split tablets before swallowing).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Neutropenia

Neutropenia was reported in patients receiving abemaciclib. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2). Fatal events of neutropenic sepsis occurred in < 1 % of patients with metastatic breast cancer. Patients should be instructed to report any episode of fever to their healthcare provider.

Infections/infestations

Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in < 1 % of patients with metastatic breast cancer. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with abemaciclib plus endocrine therapy. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate. Based on the grade of VTE, abemaciclib may require dose modification (see section 4.2).

Arterial Thromboembolic Events

A potential increased risk for serious arterial thromboembolic events (ATEs), including ischemic stroke and myocardial infarction, has been observed in metastatic breast cancer studies when abemaciclib was administered in combination with endocrine therapies. The benefits and risks of continuing abemaciclib in patients who experience a serious ATE should be considered.

Increased aminotransferases

Increases in ALT and AST were reported in patients receiving abemaciclib. Based on the level of ALT or AST elevation, abemaciclib may require dose modification (see section 4.2).

Diarrhoea

Diarrhoea is the most common adverse reaction. Across clinical studies, median time to onset of the first diarrhoea event was approximately 6 to 8 days, and median duration of diarrhoea was 7 to 12 days (Grade 2) and 5 to 8 days (Grade 3). Diarrhoea can be associated with dehydration. Patients should start treatment with antidiarrhoeal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop ≥ Grade 2 diarrhoea (see section 4.2).

ILD/Pneumonitis

ILD/pneumonitis was reported in patients receiving abemaciclib. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and treated as medically appropriate. Based on the grade of ILD/pneumonitis, abemaciclib may require dose modification (see section 4.2). Permanently discontinue abemaciclib in patients with Grade 3 or 4 ILD/pneumonitis.

Concomitant use of inducers of CYP3A4

Concomitant use of CYP3A4 inducers should be avoided due to the risk of decreased efficacy of abemaciclib (see section 4.5).

Visceral crisis

There are no data on the efficacy and safety of abemaciclib in patients with visceral crisis.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on the pharmacokinetics of abemaciclib

Abemaciclib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors
Co-administration of abemaciclib with CYP3A4 inhibitors can increase plasma concentrations of abemaciclib. In patients with advanced and/or metastatic cancer, co-administration of the CYP3A4 inhibitor clarithromycin resulted in a 3.4-fold increase in the plasma exposure of abemaciclib and a 2.5-fold increase in the combined unbound potency adjusted plasma exposure of abemaciclib and its active metabolites.

Use of strong CYP3A4 inhibitors together with abemaciclib should be avoided. If strong CYP3A4 inhibitors need to be co-administered, the dose of abemaciclib should be reduced (see section 4.2), followed by careful monitoring of toxicity. Examples of strong CYP3A4 inhibitors include, but not limited to: clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole or voriconazole. Avoid grapefruit or grapefruit juice.

No dose adjustment is necessary for patients treated with moderate or weak CYP3A4 inhibitors. There should, however, be close monitoring for signs of toxicity.

CYP3A4 inducers
Co-administration of abemaciclib with the strong CYP3A4 inducer rifampicin decreased the plasma concentration of abemaciclib by 95 % and unbound potency adjusted plasma concentration of abemaciclib plus its active metabolites by 77 % based on $AUC_{0-\infty}$. Concomitant use of strong CYP3A4 inducers (including, but not limited to: carbamazepine, phenytoin, rifampicin and St. John's wort) should be avoided due to the risk of decreased efficacy of abemaciclib.

Effects of abemaciclib on the pharmacokinetics of other medicinal products

Medicinal products that are substrates of transporters
Abemaciclib and its major active metabolites inhibit the renal transporters organic cation transporter 2 (OCT2), multidrug and extrusion toxin protein (MATE1), and MATE2-K. *In vivo* interactions of abemaciclib with clinically relevant substrates of these transporters, such as dofetilide or creatinine, may occur (see section 4.8). In a clinical drug interaction study with metformin (substrate of OCT2, MATE1 and 2) co-administered with 400 mg abemaciclib, a small but not clinically relevant increase (37 %) in metformin plasma exposure was observed. This was found to be due to reduced renal secretion with unaffected glomerular filtration.

In healthy subjects, co-administration of abemaciclib and the P-glycoprotein (P-gp) substrate loperamide resulted in an increase in loperamide plasma exposure of 9 % based on $AUC_{0-\infty}$ and 35 % based on C_{max}. This was not considered to be clinically relevant. However, based on the *in vitro* inhibition of P-gp and breast cancer resistance protein (BCRP) observed with abemaciclib, *in vivo* interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin or dabigatran etexilate, may occur.

In a clinical study in patients with breast cancer, there was no clinically-relevant pharmacokinetic drug interaction between abemaciclib and anastrozole, fulvestrant, exemestane, letrozole or tamoxifen.

It is currently unknown whether abemaciclib may reduce the effectiveness of systemically acting hormonal contraceptives.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should use highly effective contraception methods (e.g. double-barrier contraception) during treatment and for at least 3 weeks after completing therapy (see section 4.5).

Pregnancy

There are no data from the use of abemaciclib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Verzenios is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

It is unknown whether abemaciclib is excreted in human milk. A risk to breast-feeding children cannot be excluded. Patients receiving abemaciclib should not breast-feed.

Fertility

The effect of abemaciclib on fertility in humans is unknown. While in rats no effects on male fertility were noted, cytotoxic effects to the male reproductive tract in mice, rats, and dogs indicate that abemaciclib may impair fertility in males. No adverse effects on female reproductive organs in mice, rats, or dogs, nor effects on female fertility and early embryonic development in rats were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Verzenios has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with Verzenios (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, leukopenia, anaemia, fatigue, nausea, vomiting, alopecia and decreased appetite.

Of the most common adverse reactions, Grade ≥ 3 events were less than 5 % with the exception of neutropenia, leukopenia, and diarrhoea.

Tabulated list of adverse reactions

In the following table, adverse reactions are listed in order of MedDRA body system organ class and frequency. Frequency gradings are: very common (≥1 / 10), common (≥1 / 100 to < 1 / 10), uncommon (≥1 / 1 000 to < 1 / 100), rare (≥1 / 10 000 to < 1 / 1 000), very rare (< 1 / 10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 8. Adverse reactions reported in the phase 3 studies of abemaciclib in combination with endocrine therapy[a] (N = 3 559) and during post-marketing experience

System organ class	Very common	Common	Uncommon	Rare
Infections and infestations	Infections [b]			
Blood and lymphatic system disorders	Neutropenia Leukopenia Anaemia Thrombocytopenia Lymphopenia [h]		Febrile neutropenia [e]	
Metabolism and nutrition disorders	Decreased appetite			
Nervous system disorders	Headache [f] Dysgeusia [g] Dizziness [g]			
Eye disorders		Lacrimation increased	Photopsia Keratitis	
Vascular disorders		Venous thromboembolism [c]		
Respiratory, thoracic and mediastinal disorders		ILD/pneumonitis [d]		
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Stomatitis [f]	Dyspepsia [f]		
Skin and subcutaneous tissue disorders	Alopecia [g] Pruritus [g] Rash [g]	Nail disorder [f] Dry skin [e]		Erythema multiforme
Musculoskeletal and connective tissue disorders		Muscular weakness [e]		
General disorders and administration site conditions	Pyrexia [e] Fatigue			

Investigations	Alanine aminotransferase increased [g] Aspartate aminotransferase increased [g]			

[a] Abemaciclib in combination with anastrozole, letrozole, exemestane, tamoxifen, or fulvestrant.
[b] Infections include all reported preferred terms that are part of the system organ class infections and infestations.
[c] Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis.
[d] ILD/pneumonitis for early breast cancer (EBC) include all reported preferred terms that are part of the MedDRA SMQ interstitial lung disease. For metastatic breast cancer (mBC) preferred terms include interstitial lung disease, pneumonitis, organising pneumonia, pulmonary fibrosis and bronchiolitis obliterans.
[e] Considered ADRs in the mBC setting only (MONARCH 2 and MONARCH 3).
[f] Considered ADRs in the EBC setting only (monarchE).
[g] Common frequency in the EBC setting (monarchE), very common in the mBC setting (MONARCH 2 and MONARCH 3).
[h] Common frequency in mBC setting (MONARCH 2 and MONARCH 3), very common in the EBC setting (monarchE).

Description of selected adverse reactions

Neutropenia
Neutropenia was reported frequently across studies. In the monarchE study, neutropenia was reported in 45.8 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 19.1 % of patients receiving abemaciclib in combination with endocrine therapy with a median time to onset of 30 days, and median time to resolution of 16 days. Febrile neutropenia was reported in 0.3 % patients. In MONARCH 2 and MONARCH 3 studies, neutropenia was reported in 45.1 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28.2 % of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile neutropenia was reported in 0.9 % patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2).

Diarrhoea
Diarrhoea was the most commonly reported adverse reaction (see Table 8). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. In the monarchE study, the median time to onset of the first diarrhoea event of any grade was 8 days. The median duration of diarrhoea was 7 days for Grade 2 and 5 days for Grade 3. In MONARCH 2 and MONARCH 3 studies, the median time to onset of the first diarrhoea event of any grade was approximately 6 to 8 days. The median duration of diarrhoea was 9 to 12 days for Grade 2 and 6 to 8 days for Grade 3. Diarrhoea returned to baseline or lesser grade with supportive treatment such as loperamide and/or dose adjustment (see section 4.2).

Increased aminotransferases
In the monarchE study, ALT and AST elevations were reported frequently (12.3 % and 11.8 %, respectively) in patients receiving abemaciclib in combination with endocrine therapy. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 2.6 % and 1.6 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 118 days, and median time to resolution was 14.5 days. The median time to onset of Grade 3 or 4 AST elevation was 90.5 days, and median time to resolution was 11 days. In MONARCH 2 and MONARCH 3 studies, ALT and AST elevations were reported frequently (15.1 % and 14.2 %, respectively) in patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6.1 % and 4.2 % patients. The median time to onset of Grade 3

or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2).

Creatinine
Although not an adverse reaction, abemaciclib has been shown to increase serum creatinine. In the monarchE study, 99.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 0.5 % of patients had Grade 3 or 4 elevations. In patients receiving endocrine therapy alone, 91.0 % reported an increase in serum creatinine (all laboratory grades). In MONARCH 2 and MONARCH 3 studies, 98.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 1.9 % of patients had Grade 3 or 4 elevations. In patients receiving an aromatase inhibitor or fulvestrant alone, 78.4 % reported an increase in serum creatinine (all laboratory grades). Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance) (see section 4.5). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of an abemaciclib overdose, fatigue and diarrhoea may occur. General supportive care should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinases inhibitors, ATC code: L01EF03

Mechanism of action

Abemaciclib is a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), and most active against Cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking cell cycle progression from the G1 to the S-phase of cell division, leading to suppression of tumour growth. In oestrogen receptor-positive breast cancer cell lines, sustained target inhibition with abemaciclib prevented rebound of Rb phosphorylation resulting in cell senescence and apoptosis. *In vitro*, Rb-negative and Rb-depleted cancer cell lines are generally less sensitive to abemaciclib. In breast cancer xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations alone or in combination with anti-oestrogens resulted in reduction of tumour size.

Pharmacodynamic effects

In cancer patients, abemaciclib inhibits CDK4 and CDK6 as indicated by inhibition of phosphorylation of Rb and topoisomerase II alpha, which results in cell cycle inhibition upstream of the G1 restriction point.

Cardiac electrophysiology

The effect of abemaciclib on the QTcF interval was evaluated in 144 patients with advanced cancer. No large change (that is, > 20 ms) in the QTcF interval was detected at the mean observed maximal steady state abemaciclib concentration following a therapeutic dosing schedule.

In an exposure-response analysis in healthy subjects at exposures comparable to a 200 mg twice-daily dose, abemaciclib did not prolong the QTcF interval to any clinically relevant extent.

Clinical efficacy and safety

Early breast cancer

Randomised Phase 3 Study monarchE: Verzenios in combination with endocrine therapy
The efficacy and safety of Verzenios in combination with adjuvant endocrine therapy was evaluated in monarchE, a randomised, open label, two cohort, phase 3 study, in women and men with HR-positive, HER2-negative, node positive early breast cancer at high risk of recurrence. High risk of recurrence in Cohort 1 was defined by clinical and pathological features: either ≥ 4 pALN (positive axillary lymph nodes), or 1-3 pALN and at least one of the following criteria: tumor size ≥ 5 cm or histological grade 3.

A total of 5 637 patients were randomised in a 1:1 ratio to receive 2 years of Verzenios 150 mg twice daily plus physician's choice of standard endocrine therapy, or standard endocrine therapy alone. Randomization was stratified by prior chemotherapy, menopausal status, and region. Men were stratified as postmenopausal. Patients had completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy). Patients must have recovered from the acute side effects of any prior chemotherapy or radiotherapy. A washout period of 21 days after chemotherapy and 14 days after radiotherapy prior to randomization was required. Patients were allowed to receive up to 12 weeks of adjuvant endocrine therapy prior to randomisation following the last non-endocrine therapy (surgery, chemotherapy or radiation). Adjuvant treatment with fulvestrant was not allowed as standard endocrine therapy. Patients with eastern cooperative oncology group (ECOG) Performance Status 0 or 1 were eligible. Patients with history of VTEs were excluded from the study. After the end of the study treatment period, in both treatment arms patients continued to receive adjuvant endocrine therapy for a cumulative duration of at least 5 years and up to 10 years, if medically appropriate. LHRH agonists were given when clinically indicated to pre- and perimenopausal women, and men.

Among the 5 637 randomised patients, 5 120 were enrolled in Cohort 1, representing 91 % of the ITT population. In Cohort 1, patient demographics and baseline tumour characteristics were balanced between treatment arms. The median age of patients enrolled was approximately 51 years (range, 22-89 years), 15 % of patients were 65 or older, 99 % were women, 71 % were Caucasian, 24 % were Asian, and 5 % Other. Forty three percent of patients were pre- or perimenopausal. Most patients received prior chemotherapy (36 % neoadjuvant, 62 % adjuvant), and prior radiotherapy (96 %). Initial endocrine therapy received by patients included letrozole (39 %), tamoxifen (31 %), anastrozole (22 %), or exemestane (8 %).

Sixty-five percent of the patients had 4 or more positive lymph nodes, 41 % had Grade 3 tumour, and 24 % had pathological tumour size ≥ 5 cm at surgery.

The primary endpoint was invasive disease-free survival (IDFS) in ITT population defined as the time from randomization to the first occurrence of ipsilateral invasive breast tumour recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second

primary non-breast invasive cancer, or death attributable to any cause. Key secondary endpoint was distant relapse free survival (DRFS) in ITT population defined as time from randomization to the first occurrence of distant recurrence, or death attributable to any cause.

The primary objective of the study was met at the pre-planned interim analysis (16 Mar 2020 cut-off). A statistically significant improvement in IDFS was observed in patients who received Verzenios plus endocrine therapy versus endocrine therapy alone in the ITT population. At the time of the subsequent final overall survival (OS) analysis (15 July 2025 cut-off) a statistically significant improvement in OS was also observed in patients who received Verzenios plus endocrine therapy versus endocrine therapy alone in the ITT population. The approval was granted for the large subpopulation, Cohort 1.

At the final OS analysis all patients in Cohort 1 were off the 2-year study treatment period and the median duration of follow-up was 76 months (6.3 years).

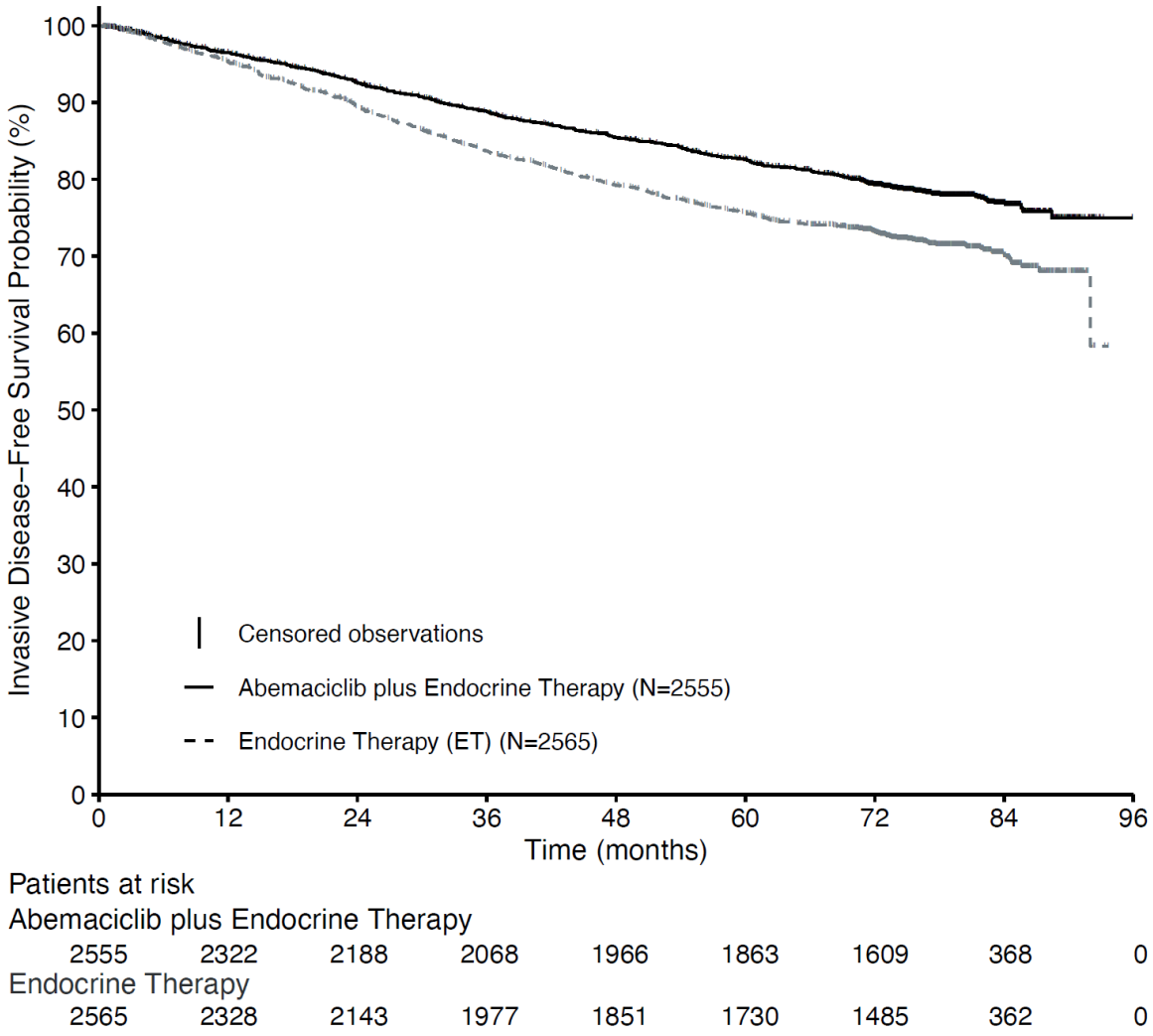
Efficacy results in Cohort 1 are summarised in Table 9, Figure 1 and Figure 2.

Table 9. monarchE: Summary of efficacy data (Cohort 1 population)

	Verzenios plus endocrine therapy N = 2 555	**Endocrine therapy alone N = 2 565**
Invasive disease-free survival (IDFS)		
Number of patients with event (n, %)	512 (20.0)	678 (26.4)
Hazard ratio (95 % CI)	0.726 (0.648, 0.815)	
IDFS at 84 months (%, 95 % CI)	77.0 (75.0, 78.8)	70.1 (68.0, 72.1)
Distant relapse free survival (DRFS)		
Number of patients with an event (n, %)	448 (17.5)	589 (23.0)
Hazard ratio (95 % CI)	0.736 (0.651, 0.832)	
DRFS at 84 months (%, 95 % CI)	79.5 (77.6, 81.2)	74.0 (72.0, 75.9
Overall Survival (OS)		
Number of events, n (%)	286 (11.2)	344 (13.4)
Hazard Ratio (95% CI)	0.835 (0.713, 0.977)	

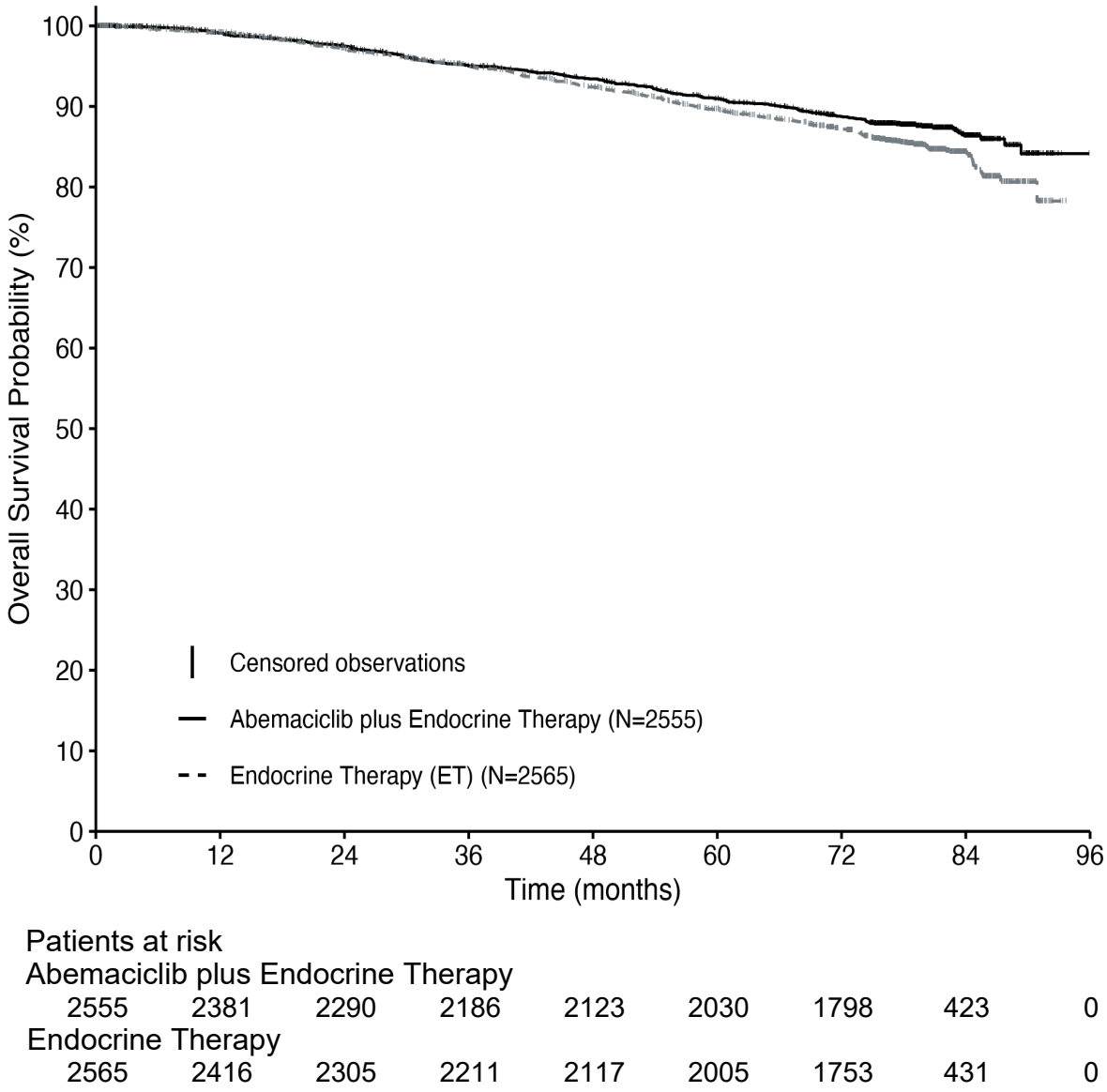
Abbreviation: CI = confidence interval.
Data cut-off date 15 July 2025

Figure 1. monarchE: Kaplan-Meier plot of IDFS (Investigator assessment, Cohort 1 population)



Abbreviations: IDFS = invasive disease-free survival; N = number of patients in the population.
Data cut-off date 15 July 2025

Figure 2. monarchE: Kaplan-Meier plot of OS (Cohort 1 population)



Abbreviations: ET = endocrine therapy; OS = overall survival; N = number of patients in the population.
Data cut-off date 15 Jul 2025

Benefit was observed across patient subgroups defined by geographic region, menopausal status and prior chemotherapy within Cohort 1.

Advanced or metastatic breast cancer

Randomised Phase 3 Study MONARCH 3: Verzenios in combination with aromatase inhibitors
The efficacy and safety of Verzenios in combination with an aromatase inhibitor (anastrozole or letrozole) was evaluated in MONARCH 3, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer who had not received prior systemic therapy in this disease setting. Patients were randomised in a 2:1 ratio to receive Verzenios 150 mg twice daily plus a non-steroidal aromatase inhibitor given daily at the recommended dose versus placebo plus a non-steroidal aromatase inhibitor according to the same schedule. The primary endpoint was investigator-assessed progression-free survival (PFS) evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

The median age of patients enrolled was 63 years (range 32 - 88). Approximately 39 % of patients had received chemotherapy and 44 % had received antihormonal therapy in the (neo)adjuvant setting. Patients with prior (neo)adjuvant endocrine therapy must have completed this therapy at least 12 months before study randomisation. The majority of patients (96 %) had metastatic disease at baseline. Approximately 22 % of patients had bone-only disease, and 53 % patients had visceral metastases.

The study met its primary endpoint of improving PFS. Primary efficacy results are summarised in Table 10 and Figure 3.

Table 10. MONARCH 3: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	Verzenios plus aromatase inhibitor	**Placebo plus aromatase inhibitor**
Progression-free survival	**N = 328**	**N = 165**
Investigator assessment, number of events (%)	138 (42.1)	108 (65.5)
Median [months] (95 % CI)	28.18 (23.51, NR)	14.76 (11.24, 19.20)
Hazard ratio (95 % CI) and p-value	0.540 (0.418, 0.698), p = 0.000002	
Independent radiographic review, number of events (%)	91 (27.7)	73 (44.2)
Median [months] (95 % CI)	NR (NR, NR)	19.36 (16.37, 27.91)
Hazard ratio (95 % CI) and p-value	0.465 (0.339, 0.636); p < 0.000001	
Objective response rate[b] [%] (95 % CI)	49.7 (44.3, 55.1)	37.0 (29.6, 44.3)
Duration of response [months] (95 % CI)	27.39 (25.74, NR)	17.46 (11.21, 22.19)
Objective response for patients with measurable disease[a]	**N = 267**	**N = 132**
Objective response rate[b] [%] (95 % CI)	61.0 (55.2, 66.9)	45.5 (37.0, 53.9)
Complete response, (%)	3.4	0
Partial response, (%)	57.7	45.5
Clinical benefit rate[c] **(measurable disease)** [%] (95 % CI)	79.0 (74.1, 83.9)	69.7 (61.9, 77.5)

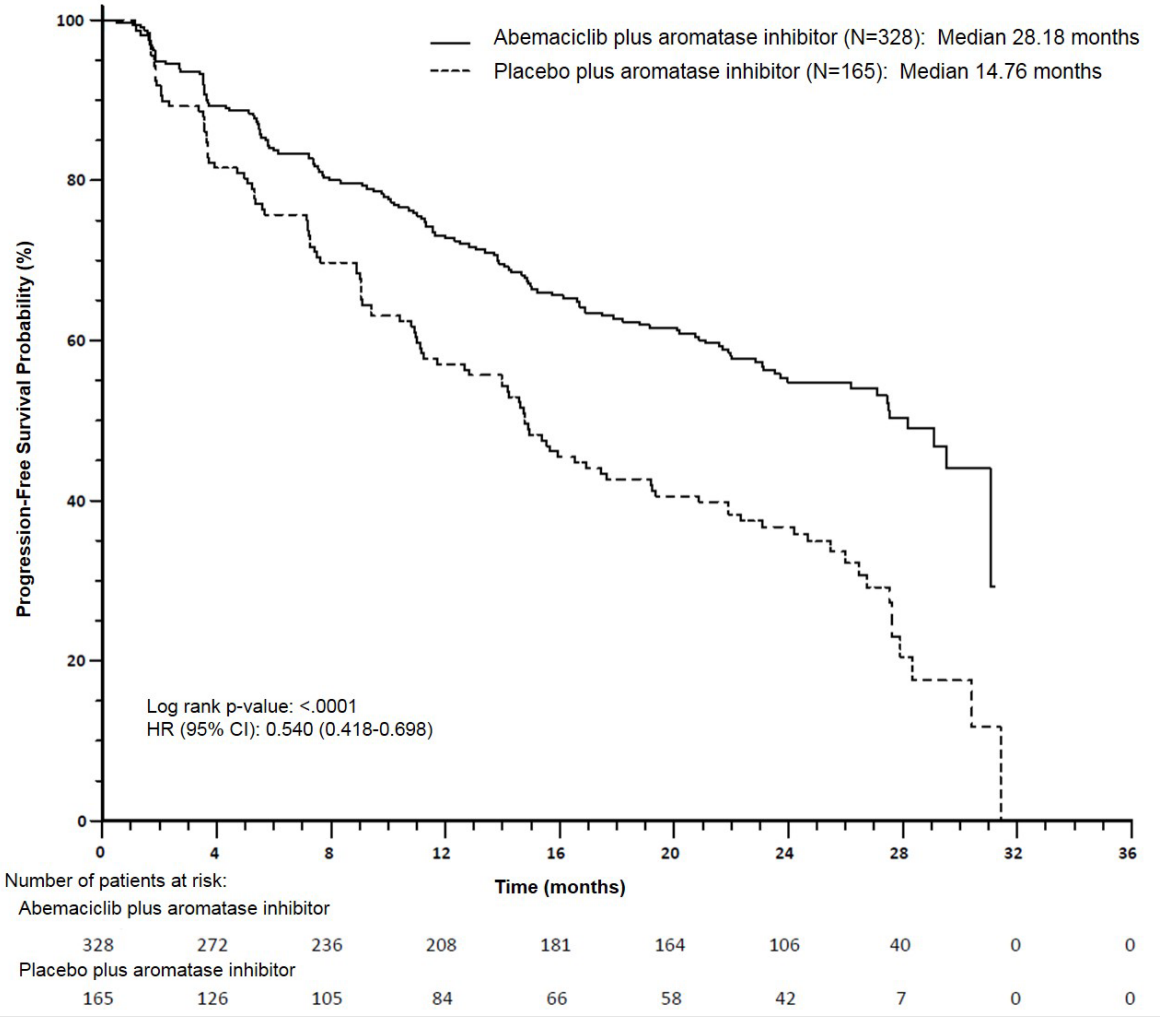
[a] Measurable disease defined per RECIST version 1.1

[b] Complete response + partial response

[c] Complete response + partial response + stable disease for ≥ 6 months

N = number of patients; CI = confidence interval; NR = not reached.

Figure 3. MONARCH 3: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 46 % for patients treated with abemaciclib plus an aromatase inhibitor.

OS was not mature at the final PFS analysis (93 events observed across the two arms). The HR was 1.057 (95 % CI: 0.683, 1.633), p = 0.8017.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or ≥ 65 years), disease site, disease setting (de novo metastatic vs recurrent metastatic vs locally advanced recurrent), presence of measurable disease, progesterone receptor status, and baseline ECOG performance status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.567 [95 % CI: 0.407, 0.789]), median PFS 21.6 months versus 14.0 months; in patients with bone-only disease (HR of 0.565 [95 % CI: 0.306, 1.044]); and in patients with measurable disease (HR of 0.517 [95 % CI: 0.392, 0.681]).

At the first OS interim analysis, 197 events were observed across the two arms and the HR was 0.786 (95 % CI: 0.589, 1.049).

At the second OS interim analysis, 255 events were observed across the two arms and the HR was 0.754 (95 % CI: 0.584, 0.974).

The results from the Final OS analysis were not statistically significant (summarised in Table 11 and Figure 4).

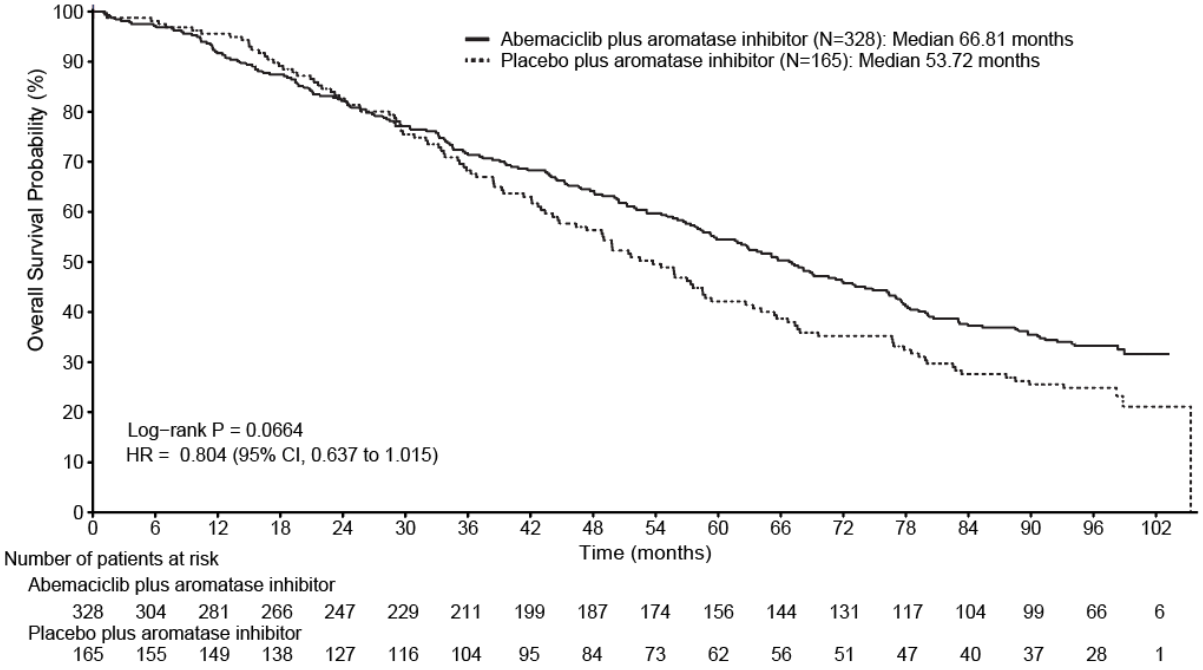
Table 11.: MONARCH 3: Summary of Overall Survival data (Intent-to-Treat Population)

	Verzenios plus Anastrozole or Letrozole	Placebo plus Anastrozole or Letrozole
Overall survival	N = 328	N = 165
Number of events (n, %)	198 (60.4)	116 (70.3)
Median OS [months] (95% CI)	66.81 (59.21, 74.83)	53.72 (44.75, 59.34)
Hazard ratio (95% CI)	0.804 (0.637, 1.015)	

Abbreviations: N = number of patients; CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

Analyses for OS in patients with visceral disease showed an OS HR of 0.758 (95% CI: 0.558, 1.030). Median OS was 63.72 months in the abemaciclib plus AI arm and 48.82 months in the placebo plus AI arm. Similar to the ITT population, the results were not statistically significant.

Figure 4. MONARCH 3: Kaplan-Meier plot of overall survival (Intent-to-treat population)



Randomised Phase 3 Study MONARCH 2: Verzenios in combination with fulvestrant
The efficacy and safety of Verzenios in combination with fulvestrant was evaluated in MONARCH 2, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer. Patients were randomised in a 2:1 ratio to receive Verzenios 150 mg twice daily plus fulvestrant 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose, versus placebo plus fulvestrant according to the same schedule. The primary endpoint was investigator-assessed PFS evaluated according to RECIST 1.1; key secondary efficacy endpoints included ORR, CBR and OS.

The median age of patients enrolled was 60 years (range, 32 - 91 years). In each treatment arm the majority of patients were white, and had not received chemotherapy for metastatic disease. 17 % of patients were pre/perimenopausal on ovarian suppression with a GnRH agonist. Approximately 56 % patients had visceral metastases. Approximately 25 % of patients had primary endocrine resistance (progression on endocrine therapy within the first 2 years of adjuvant endocrine therapy or within the first 6 months of first line endocrine therapy for metastatic breast cancer) and for the majority, endocrine resistance developed later. 59 % of patients had most recent endocrine therapy in the (neo)adjuvant setting, and 38 % in metastatic setting.

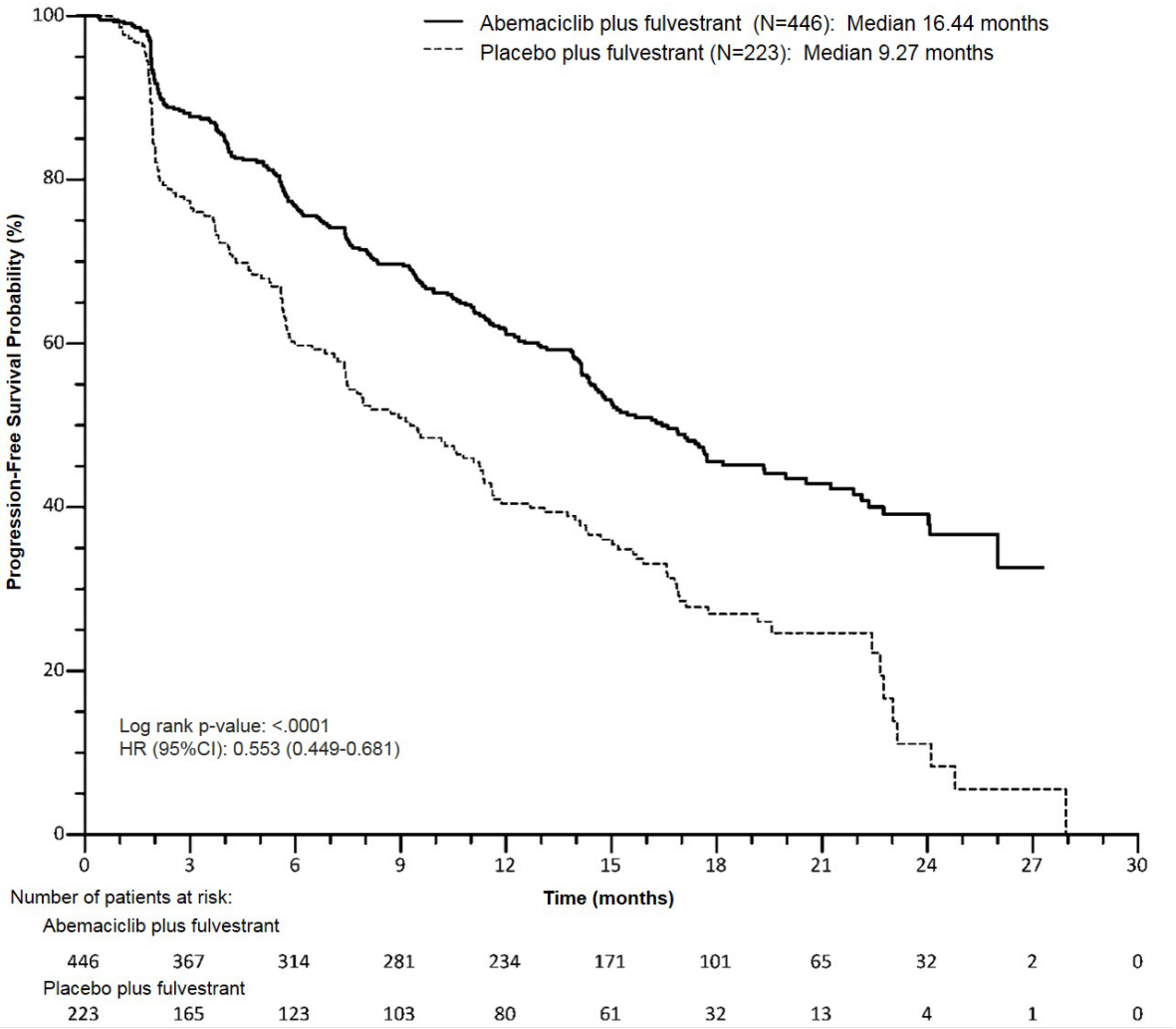
The study met its primary endpoint of improving PFS. Primary efficacy results are summarised in Table 12 and Figure 5.

Table 12. MONARCH 2: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	Verzenios plus fulvestrant	**Placebo plus fulvestrant**
Progression-free survival	**N = 446**	**N = 223**
Investigator assessment, number of events (%)	222 (49.8)	157 (70.4)
Median [months] (95 % CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95 % CI) and p-value	0.553 (0.449, 0.681), p = 0.0000001	
Independent radiographic review, number of events (%)	164 (36.8)	124 (55.6)
Median [months] (95 % CI)	22.4 (18.3, NR)	10.2 (5.8, 14.0)
Hazard ratio (95 % CI) and p-value	0.460 (0.363, 0.584); p < 0.000001	
Objective response rate[b] [%] (95 % CI)	35.2 (30.8, 39.6)	16.1 **(**11.3, 21.0)
Duration of response [months] (95 % CI)	NR (18.05, NR)	25.6 (11.9, 25.6)
Objective response for patients with measurable disease[a]	**N = 318**	**N = 164**
Objective response rate[b] [%] (95 % CI)	48.1 (42.6, 53.6)	21.3 (15.1, 27.6)
Complete response, (%)	3.5	0
Partial response, (%)	44.7	21.3
Clinical benefit rate[c] **(measurable disease)** [%] (95 % CI)	73.3 (68.4, 78.1)	51.8 (44.2, 59.5)

[a] Measurable disease defined per RECIST version 1.1
[b] Complete response + partial response
[c] Complete response + partial response + stable disease for ≥ 6 months
N = number of patients; CI = confidence interval; NR = not reached.

Figure 5. MONARCH 2: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 44.7 % for patients treated with Verzenios plus fulvestrant. Verzenios plus fulvestrant prolonged progression-free survival with neither a clinically meaningful, or significant detriment to health-related quality of life.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, disease site, endocrine therapy resistance, presence of measurable disease, progesterone receptor status, and menopausal status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.481 [95 %CI: 0.369, 0.627]), median PFS 14.7 months versus 6.5 months; in patients with bone-only disease (HR of 0.543 [95 % CI: 0.355, 0.833]); patients with measurable disease (HR of 0.523 [95 % CI: 0.412, 0.644]). In patients who were pre/perimenopausal, the hazard ratio was 0.415 (95 % CI: 0.246, 0.698); in patients who were progesterone receptor negative, the HR was 0.509 (95 % CI: 0.325, 0.797).

In a sub-population with locally advanced or metastatic disease that had not received prior endocrine therapy, the PFS was also consistent.

At the pre-specified interim OS analysis (20 June 2019 cut-off), the ITT population showed a statistically significant improvement in patients receiving Verzenios plus fulvestrant compared with those receiving placebo plus fulvestrant. The OS results are summarized in Table 13.

Table 13. MONARCH 2: Summary of overall survival data (Intent-to-treat population)

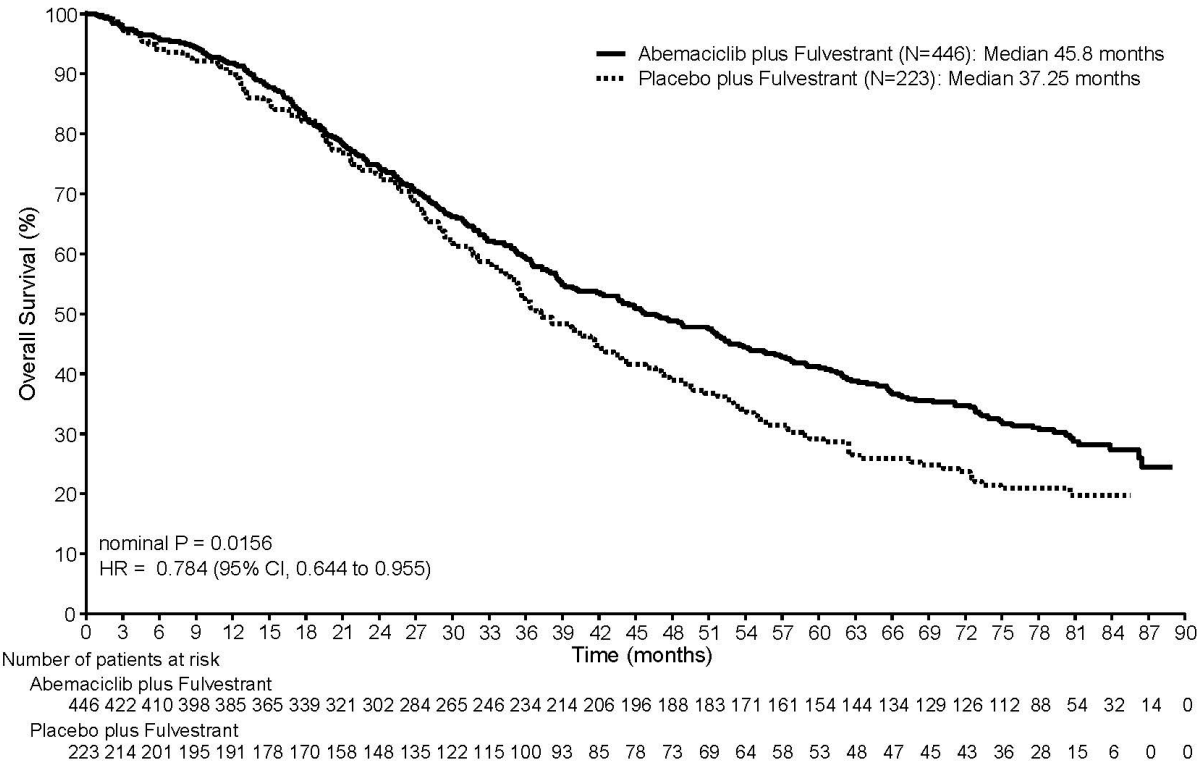
	Verzenios plus fulvestrant	Placebo plus fulvestrant
Overall survival	N = 446	N = 223
Number of events (n, %)	211 (47.3)	127 (57.0)
Median OS [months] (95 % CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95 % CI)	0.757 (0.606, 0.945)	
p-value	0.0137	

N = number of patients; CI = confidence interval; OS = overall survival

Analyses for OS by stratification factors showed OS HR of 0.675 (95 % CI: 0.511, 0.891) in patients with visceral disease, and 0.686 (95 % CI: 0.451, 1.043) in patients with primary endocrine resistance.

At the pre-specified final OS analysis (18 March 2022 cut-off), 440 events were observed across the 2 arms. The improvement in OS previously observed at the interim OS analysis (20 June 2019 cut-off) was maintained in the abemaciclib plus fulvestrant arm compared to the placebo plus fulvestrant arm, with a HR of 0.784 (95 % CI: 0.644, 0.955). Median OS was 45.8 months in the abemaciclib plus fulvestrant arm and 37.25 months in the placebo plus fulvestrant arm. The OS results are presented in Figure 6.

Figure 6. MONARCH 2: Kaplan-Meier plot of overall survival (Intent-to-treat population)



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Verzenios in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

The efficacy and safety of Verzenios in combination with irinotecan and temozolomide was evaluated in Study J1S-MC-JP04, a multicentre, randomised, open-label, phase 2 study in participants with relapsed or refractory Ewing sarcoma. The primary endpoint was progression-free survival (PFS)

assessed by a blinded independent review committee. 46 participants, 3 to 35 years of age, were randomised to receive Verzenios plus irinotecan and temozolomide or irinotecan and temozolomide in a 2:1 ratio. 58.7 % of patients (27 patients) were < 18 years of age. 45 participants were treated in 21-day cycles until disease progression or having met other discontinuation criteria. No difference in PFS was observed with the addition of Verzenios. The median PFS was 2.8 months in patients treated with Verzenios in combination irinotecan and temozolomide and 2.9 months in patients treated with irinotecan and temozolomide (HR 0.64 [95% CI: 0.28, 1.45]).

5.2 Pharmacokinetic properties

Absorption

Abemaciclib absorption is slow, with a T_{max} of 8 hours and a mean absolute bioavailability of approximately 45 %. In the therapeutic dose range of 50 - 200 mg, the increase in plasma exposure (AUC) and C_{max} is approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and abemaciclib accumulated with a geometric mean accumulation ratio of 3.7 (58 % CV) and 5.8 (65 % CV) based on C_{max} and AUC, respectively. A high-fat meal increased combined AUC of abemaciclib and its active metabolites by 9 % and increased C_{max} by 26 %. These changes were not considered to be clinically relevant. Therefore, abemaciclib can be taken with or without food.

Distribution

Abemaciclib is highly bound to plasma proteins in humans (mean bound fraction approximately 96 % to 98 %). The geometric mean systemic volume of distribution is approximately 750 L (69 % CV), indicating distribution of abemaciclib into tissues.

Concentrations of abemaciclib and its active metabolites in cerebrospinal fluid are comparable to unbound plasma concentrations.

Biotransformation

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolised to several metabolites primarily by cytochrome P450 (CYP) 3A4. The primary biotransformation is hydroxylation to a metabolite that circulates with an AUC that is 77 % of parent drug. In addition, N-desethyl and N-desethylhydroxy metabolites circulate at AUCs that are 39 % and 15 % of parent drug. These circulating metabolites are active with similar potency to abemaciclib.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib was 21.8 L/h (39.8 % CV), and the mean plasma elimination half-life for abemaciclib in patients was 24.8 hours (52.1 % CV). After a single oral dose of [^{14}C] -abemaciclib, approximately 81 % of the dose was excreted in faeces and 3.4 % excreted in urine. The majority of the dose eliminated in faeces was metabolites.

Special populations

Age, gender, and body weight
Age, gender, and body weight had no effect on the exposure of abemaciclib in a population pharmacokinetic analysis in patients with cancer (135 males and 859 females; age range 24 - 91 years; and body weight range 36 - 175 kg).

Hepatic impairment
Abemaciclib is metabolised in the liver. Mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had no effect on the exposure of abemaciclib. In subjects with severe hepatic impairment (Child Pugh C), the $AUC_{0-\infty}$ of abemaciclib and potency adjusted unbound abemaciclib plus its active

metabolites increased 2.1-fold and 2.4-fold, respectively. The half-life of abemaciclib increased from 24 to 55 hours (see section 4.2).

Renal impairment
Renal clearance of abemaciclib and its metabolites is minor. Mild and moderate renal impairment had no effect on the exposure of abemaciclib. There are no data in patients with severe renal impairment, end stage renal disease or in patients on dialysis.

5.3 Preclinical safety data

The primary target organ findings of potential relevance to humans occurred in the gastrointestinal tract, haematolymphopoietic organs, and male reproductive tract in mice, rats and dogs in studies up to 13 weeks duration. Effects in eyes and heart valves occurred only in rodents at clinically relevant exposure levels. Effects in lung and skeletal muscle occurred only in rodents at exposure levels at least 2-fold higher than human exposure levels. Effects in kidney occurred only in rodents at exposure levels at least 6-fold higher than human exposure levels. Complete or partial recovery was observed for all target organ findings at the end of the 28 - day recovery period, with the exception of male reproductive tract effects.

Genotoxicity

Abemaciclib was not mutagenic in a bacterial reverse mutation (Ames) assay, was not clastogenic in an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

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.

Impairment of fertility

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.

Developmental toxicity

Abemaciclib was teratogenic and caused decreased foetal weight at maternal exposures similar to the recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Lactose monohydrate
Microcrystalline cellulose
Colloidal hydrated silica
Sodium stearyl fumarate

Film coating

Verzenios 50 mg film-coated tablets
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)

Verzenios 100 mg film-coated tablets
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)

Verzenios 150 mg film-coated tablets
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PCTFE/PE/PVC blisters sealed with an aluminium foil in packs of 14, 28, 42, 56, 70 or 168 film-coated tablets.

Aluminium/aluminium perforated unit dose blisters of 28 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1307/001
EU/1/18/1307/002
EU/1/18/1307/003
EU/1/18/1307/004
EU/1/18/1307/005
EU/1/18/1307/006
EU/1/18/1307/007
EU/1/18/1307/008
EU/1/18/1307/009
EU/1/18/1307/010
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EU/1/18/1307/016
EU/1/18/1307/017
EU/1/18/1307/018
EU/1/18/1307/019
EU/1/18/1307/020
EU/1/18/1307/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2018
Date of latest renewal: 23 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Lilly, S.A.
Avda. de la Industria, 30
28108 Alcobendas, Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 50 mg film-coated tablets
abemaciclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg abemaciclib.

3. LIST OF EXCIPIENTS

Excipients: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 x 1 film-coated tablets
28 film-coated tablets
42 film-coated tablets
56 film-coated tablets
70 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1307/001 (14 film-coated tablets)
EU/1/18/1307/002 (168 film-coated tablets)
EU/1/18/1307/003 (28 x 1 film-coated tablets)
EU/1/18/1307/010 (28 film-coated tablets)
EU/1/18/1307/011 (56 film-coated tablets)
EU/1/18/1307/016 (42 film-coated tablets)
EU/1/18/1307/017 (70 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Verzenios 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 50 mg tablets
abemaciclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

Morning
Evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER FOR 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 50 mg tablets
abemaciclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 100 mg film-coated tablets
abemaciclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg abemaciclib.

3. LIST OF EXCIPIENTS

Excipients: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 x 1 film-coated tablets
28 film-coated tablets
42 film-coated tablets
56 film-coated tablets
70 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1307/004 (14 film-coated tablets)
EU/1/18/1307/005 (168 film-coated tablets)
EU/1/18/1307/006 (28 x 1 film-coated tablets)
EU/1/18/1307/012 (28 film-coated tablets)
EU/1/18/1307/013 (56 film-coated tablets)
EU/1/18/1307/018 (42 film-coated tablets)
EU/1/18/1307/019 (70 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Verzenios 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 100 mg tablets
abemaciclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

Morning
Evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 100 mg tablets
abemaciclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 150 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 150 mg film-coated tablets
abemaciclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg abemaciclib.

3. LIST OF EXCIPIENTS

Excipients: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 x 1 film-coated tablets
28 film-coated tablets
42 film-coated tablets
56 film-coated tablets
70 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1307/007 (14 film-coated tablets)
EU/1/18/1307/008 (168 film-coated tablets)
EU/1/18/1307/009 (28 x 1 film-coated tablets)
EU/1/18/1307/014 (28 film-coated tablets)
EU/1/18/1307/015 (56 film-coated tablets)
EU/1/18/1307/020 (42 film-coated tablets)
EU/1/18/1307/021 (70 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Verzenios 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 150 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 150 mg tablets
abemaciclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

Morning
Evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER FOR 150 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Verzenios 150 mg tablets
abemaciclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Verzenios 50 mg film-coated tablets
Verzenios 100 mg film-coated tablets
Verzenios 150 mg film-coated tablets
abemaciclib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Verzenios is and what it is used for

Verzenios is a cancer medicine containing the active substance abemaciclib.

Abemaciclib blocks the effects of proteins called cyclin-dependent kinase 4 and 6. These proteins are abnormally active in some cancer cells and make them grow out of control. Blocking the action of these proteins can slow down growth of cancer cells, shrink the tumour and delay progression of the cancer.

Verzenios is used to treat certain types of breast cancer (hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-)) which have:
- spread to the lymph nodes of the armpit, with no detectable spread to other parts of the body, been surgically removed, and have certain characteristics that increase the risk of the cancer returning. Treatment is given in combination with hormonal therapy, such as aromatase inhibitors or tamoxifen, to prevent the cancer from coming back after surgery (treatment after surgery is called adjuvant therapy)
- spread beyond the original tumour and/or to other organs. It is given together with hormonal therapies, such as aromatase inhibitors or fulvestrant.

2. What you need to know before you take Verzenios

Do not take Verzenios:
- if you are allergic to abemaciclib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Verzenios may:
- reduce the number of your white blood cells, and you may be at greater risk of getting an infection. Serious infections such as lung infections can be life-threatening;
- cause blood clots in the veins;
- cause severe or life-threatening inflammation of the lungs;
- affect the way your liver works;
- cause diarrhoea. At the first sign of diarrhoea, start treatment with antidiarrhoeal agents, such as loperamide. Drink plenty of fluids;
- cause blood clots in the arteries in patients also receiving hormone therapies.

See section 4 "Possible side effects", and talk to your doctor if you have any symptoms.

What your doctor will check before and during your treatment
You will have regular blood tests before and during treatment to check whether Verzenios affects your blood (white blood cells, red blood cells, platelets) or the concentration in your blood of enzymes from your liver.

Children and adolescents
Verzenios is not to be used in children and adolescents under 18 years of age.

Other medicines and Verzenios
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell you doctor or pharmacist before taking Verzenios if you are taking the following:
- medicines that may increase the concentration of Verzenios in the blood:
    - **Clarithromycin** (antibiotic used to treat bacterial infections)
    - **Itraconazole, ketoconazole, posaconazole, voriconazole** (used to treat fungal infections)
    - **Lopinavir/ritonavir** (used to treat HIV/AIDS)
    - **Digoxin** (used to treat heart disorders)
    - **Dabigatran etexilate** (used to reduce the risk of stroke and blood clots)
- medicines that may reduce the effectiveness of Verzenios:
    - **Carbamazepine** (anti-epileptic used to treat seizures or fits)
    - **Rifampicin**, used to treat tuberculosis (TB)
    - **Phenytoin** (used to treat seizures)
    - **St. John's wort** (a herbal product used to treat mild depression and anxiety)

Verzenios with food and drink
Avoid grapefruit or grapefruit juice while you are taking the medicine as they may increase the concentration of Verzenios in the blood.

Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You should not use Verzenios if you are pregnant.

You should avoid becoming pregnant while taking Verzenios.

If you are able to have children, you should use adequate contraceptive methods (e.g., double –barrier contraception such as condom and diaphragm) during therapy and for at least 3 weeks after completing therapy. Discuss contraception with your doctor if there is any possibility that you may become pregnant.

You must tell your doctor if you become pregnant.

Breast-feeding
You should not breast-feed while taking Verzenios. It is not known if Verzenios passes into breast milk.

Fertility
Verzenios may decrease fertility in men. Talk to your doctor to seek advice about fertility prior to treatment.

Driving and using machines
Tiredness and dizziness are very common side effects. If you feel unusually tired or dizzy, take special care when driving or using machines.

Verzenios contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Verzenios contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Verzenios

Recommended dose
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

When given together with endocrine therapy to treat your breast cancer, the recommended dose of Verzenios is 150 mg taken by mouth twice daily.

If you get certain side effects while you are taking Verzenios your doctor may lower your dose or stop treatment temporarily or permanently.

When and how to take Verzenios
Take Verzenios twice daily, at about the same time every day, preferably in the morning and evening, so there is enough medicine in your body all the time.

You can take the tablets either with or without food, just avoid grapefruit and grapefruit juice (see section 2 "Verzenios with food and drink").

Swallow the tablet whole with a glass of water. Do not chew, crush or split the tablets before swallowing.

How long to take Verzenios
Take Verzenios continuously for as long as your doctor tells you to. If you take Verzenios for early breast cancer treatment, you should take it for up to 2 years.

If you take more Verzenios than you should
If you take too many tablets, or if someone else takes your medicine, contact a doctor or hospital for advice. Show the Verzenios carton and this leaflet. Medical treatment may be necessary.

If you miss a dose of Verzenios
If you vomit after taking the dose or forget a dose, take your next dose at your usual time. Do not take a double dose to make up for the forgotten or vomited dose.

If you stop taking Verzenios
Do not stop taking Verzenios unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side-effects, although not everybody gets them. Contact your doctor immediately for any of the following:

- Symptoms such as chills or fever. These could be a sign of low white blood cell counts (which may affect more than 1 in 10 people) and should be treated immediately. If you have cough, fever and difficulty breathing or chest pain, this could be a sign of lung infection. Serious or life-threatening infections are uncommon (may affect up to 1 in 100 people).
- Painful swollen leg, chest pain, shortness of breath, rapid breathing or rapid heart rate as these can be signs of blood clots in the vein (which may affect up to 1 in 10 people).
- Diarrhoea (which may affect more than 1 in 10 people).

Refer to section 2 for more information on any of the possible effects listed above.

Other side effects with Verzenios may include:

Very common side effects (may affect more than 1 in 10 people)

- Infections
- Reduction in white blood cells, red blood cells, and blood platelets
- Nausea (feeling sick), vomiting
- Inflammation or sore mouth
- Decreased appetite
- Headache
- Alteration in sense of taste
- Hair loss
- Tiredness
- Dizziness
- Itching
- Rash
- Abnormalities in liver blood tests

Common side effects (may affect up to 1 in 10 people)

- Watering eyes
- Muscular weakness
- Dry skin
- Inflammation of the lungs which causes breathlessness, cough and raised temperature
- Indigestion or upset stomach
- Nail disorders such as breaking or splitting of nails

Uncommon side effects (may affect up to 1 in 100 people)
- Low levels of white blood cells with fever
- Perception of flashes of light or floaters in your vision
- Keratitis (inflammation of the Cornea)

Rare side effects (may affect up to 1 in 1000 people)
- A skin reaction that causes red spots or patches on the skin that may look like a target or "bullseye" with a dark red centre surrounded by paler red rings (erythema multiforme).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Verzenios

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Verzenios contains
- The active substance is abemaciclib. Verzenios film-coated tablets come in different strengths:
  - Verzenios 50 mg film-coated tablet: each tablet contains 50 mg abemaciclib.
  - Verzenios 100 mg film-coated tablet: each tablet contains 100 mg abemaciclib.
  - Verzenios 150 mg film-coated tablet: each tablet contains 150 mg abemaciclib.

- The other ingredients in this medicine are:
  - Tablet core: colloidal hydrated silica, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate (see section 2 under 'Verzenios contains lactose' and 'Verzenios contains sodium' for further information).
  - Film-coating: titanium dioxide (E171), talc (E553b), polyvinyl alcohol (E1203), macrogol 3350 (E1521), iron oxide yellow (E172) [50 mg and 150 mg tablets only], iron oxide red (E172) [50 mg tablets only].

What Verzenios looks like and contents of the pack
- Verzenios 50 mg film-coated tablets are beige, oval tablets debossed with "Lilly" on one side and "50" on the other.
- Verzenios 100 mg film-coated tablets are white, oval tablets debossed with "Lilly" on one side and "100" on the other.
- Verzenios 150 mg film-coated tablets are yellow, oval tablets debossed with "Lilly" on one side and "150" on the other.

Verzenios is available in calendar blister packs of 14, 28, 42, 56, 70 and 168 film-coated tablets and perforated unit dose blisters of 28 x 1 film-coated tablets.

Not all the pack sizes may be marketed.

Marketing Authorisation Holder
Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

Manufacturer
Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.