EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/551438/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Verzenios

International non-proprietary name: abemaciclib

Procedure No. EMEA/H/C/004302/0000

Note

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

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List of abbreviations

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
BE	Bioequivalence
BID	twice daily
CBR	clinical benefit rate (complete response + partial response + stable disease ≥6 months)
CDK	cyclin-dependent kinase
CDK4 and CDK6	cyclin-dependent kinases 4 and 6
CI	confidence interval
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CRF	clinical report form; also called case report form
CSR	clinical study report
CTAB	cetyltrimethylammonium bromide
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOP1	Division on Oncology Products 1
DoR	duration of response
DS	design space
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
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	estrogen receptor
ER +/-	estrogen receptor positive/negative
FaSSIF	fasted state simulated intestinal fluid
FDA	Food and Drug Administration
FF NIR	feed frame near infrared
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
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
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.
IPC	in-process control
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.
NDA	New Drug Application
NOR	normal operating range
NR	not reported
NSAIs	non-steroidal aromatase inhibitors
ORR	objective response rate
OS	overall survival
PAR	proven acceptable range
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetic
PopPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
Q12H	every 12 hours
QbD	quality by design
PAT	process analytical technology
RECIST	Response Evaluation Criteria in Solid Tumors
responder	any patient who exhibited a confirmed complete response or partial response per Response Evaluation Criteria in Solid Tumors version 1.1.
RTRT	real time release testing
SAE	serious adverse event(s)
SBS	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	stable disease
SOC	system organ class
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
US/USA	United States / United States of America

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 27 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Verzenios, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2015.

The applicant applied for the following indication:

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 as initial endocrine-based therapy
- in combination with fulvestrant as initial endocrine-based therapy, or following endocrine therapy
- as monotherapy following disease progression after endocrine therapy and one or two

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance abemaciclib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product

previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	**date**	**Area**
EMA/CHMP/SWAP/140264/2014	20 March 2014	quality, non-clinical and clinical
EMA/CHMP/SWAP/566558/2015	24 September 2015	clinical

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: Daniela Melchiorri

The application was received by the EMA on	27 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 December 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	04 April 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses	14 June 2018

to the List of Outstanding Issues to all CHMP members on	
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	25 June 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 June 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	02 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Verzenios on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication for Verzenios is 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 as initial endocrine-based therapy
- in combination with fulvestrant as initial endocrine-based therapy, or following endocrine therapy
- as monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting.

2.1.2. Epidemiology

Breast cancer is the second most common cancer in the world and the most frequent among women. An estimated 1.67 million women were diagnosed with breast cancer worldwide in 2012 (representing around 25% of all cancers in women) and approximately 522,000 deaths were recorded (Ferlay et. al., Int J Cancer, 2012).

2.1.3. 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.

2.1.4. Stage and prognosis

Metastatic breast cancer is an incurable disease with a median overall survival of ~2- 3 years and a 5-year survival of only ~25%. The targeted population is advanced and metastatic breast cancer patients with tumours expressing the estrogen receptor (ER), but not the HER2-receptor. Median overall survival in this subgroup is better, ~2.5-4 years. Of new breast cancer cases diagnosed worldwide each year, roughly 60% to 65% are HR-positive, 20% to 25% are HER2-positive, and 15% to 18% are triple-negative. The expression profile of biological markers in breast cancer is correlated with prognosis and response to treatment, and therefore plays an important role in treatment decisions.

2.1.5. Management

Locally advanced or metastatic breast cancer patients derive benefit mainly from systemic treatments. In this setting therapy rarely has a curative intent, and patients eventually die from the disease. For the targeted population, a variety of endocrine therapies such as letrozole, anastrozole, exemestane, fulvestrant and tamoxifen are valid 1st line options. It is reasonable to consider the choice of endocrine therapy mainly a reflection of greater tolerability compared to chemotherapy, as there is no high-level evidence demonstrating an efficacy advantage. TTP/PFS in the range of 5- 15 (20) months is typical in endocrine therapy trials in the postmenopausal population.

In September 2016 a first in class cyclin dependent kinase (CDK) 4/6 inhibitor, Ibrance (palbociclib), received a positive opinion from the CHMP, as an add-on to endocrine therapy. A second CDK 4/6 inhibitor, Kisqali (ribociclib), received a positive opinion in June 2017:

Indication	**Efficacy**	**Selected grade 3/4 adverse events**
Ibrance (palbociclib)		
Ibrance is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer: - in combination with an aromatase inhibitor; - in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1). In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.	PALOMA-2: PFS 25 vs. 15 months HR 0.58 (p < 0.000001) PALOMA-3: PFS 11 vs. 4.6 months HR 0.50 (p < 0.000001)	Neutropenia 56% - 48% ALT/AST ↑ 2.3%/2.5% - 1.9%/3.9% Fatigue 1.8% - 2.0% Diarrhea 1.4% - 0% QTc > 500 ms - 0.3%
PALOMA-2: palbociclib add-on to letrozole in ER+ HER2- breast cancer, 1st line postmenopausal. PALOMA-3: palbociclib add-on to fulvestrant (+LHRH agonist if not postmenopausal) in ER+ HER2- breast cancer with		

progression on endocrine therapy (< 12 months adjuvant, < 1 month advanced).		
Kisqali (ribociclib)		
Kisqali in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy.	MONALEESA-2: PFS 25 vs. 16 months HR 0.57 ($p = 9.6 \times 10^{-8}$)	Neutropenia 48% ALT/AST ↑ 9.3% /5.7% Fatigue 2.4% Diarrhea 1.2% QTc > 500 ms 0.3%
MONALEESA-2: ribociclib add-on to letrozole in ER+ HER2- breast cancer, 1st line postmenopausal.		
Verzenios (abemaciclib)		
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. -	MONARCH-3: PFS 28.18 vs. 14.8 months HR 0.54 (p = 0.000002) MONARCH-2: PFS 16.4 vs. 9.3 months HR 0.55 (p < 0.0000001)	Neutropenia 28% ALT/AST ↑ 5.1/2.9% Fatigue - 2.7 % Diarrhea 11.7%
MONARCH-3: abemaciclib add-on to NSAI in ER+ HER2- breast cancer, 1st line postmenopausal. MONARCH-2: abemaciclib add-on to fulvestrant (+GNRH agonist if not postmenopausal) in ER+ HER2- breast cancer with progression on endocrine therapy in the (neo) adjuvant (< 12 months) or metastatic setting.		

Endocrine refractoriness eventually develops. Single agent chemotherapy is preferred, as no overall survival benefit has been demonstrated for combinations. Anthracyclines or taxanes would usually be considered 1st line, if not administered in the (neo) adjuvant setting. Capecitabine and vinorelbine are options for patients that have received anthracyclines or taxanes, and can thus be used in the 1st or 2nd line metastatic setting. Eribulin is approved for breast cancer patients who have progressed after ≥1 chemotherapeutic regimen for advanced disease, and have previously received an anthracycline and a taxane.

Alternative treatments for the targeted monotherapy population (applicant's selection):

Drug	N	ORR		SD	PD	CBR 6 months	DOR months	PFS months	OS months
		CR	PR						
Abemaciclib	132	0	20%	48%	26%	42%	8.6	6.0	22
Eribulin[a]	508	1%	12%	44%	41%	23%	4.2	3.7	13
TPC[a]	254	0	5%	45%	49%	17%	6.7	2.2	11
Eribulin[b]	554	0.2%	11%	57%	23%	26%	6.5	4.1	16
Capectitabine[b]	548	0	12%	55%	24%	27%	11	4.2	15

Ixabepilone[c]	126	0	18%	44%	29%	14%	5.7	3.1	8.6
[a]Cortes et. al., Lancet 2011;377(9769):914-923, [b]Kaufman et. al., J Clin Oncol 2015;33(6):594-601, [c]Perez et. al., J Clin Oncol 2007;25(23):3407-3414. NR = not reported.									

2.2. About the product

Abemaciclib is an orally administered small-molecule inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). 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.

The applicant is seeking approval of abemaciclib for the following proposed indications:

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 as initial endocrine-based therapy
- in combination with fulvestrant as initial endocrine-based therapy, or following endocrine therapy
- as monotherapy following disease progression after endocrine therapy and one or two chemotherapy regimens in the metastatic setting.

Verzenios in combination with endocrine therapy

The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. In the Summary of Product Characteristics (section 4.2), reference is made to the SmPC of the endocrine therapy combination partner for a recommended posology. Women treated with the combination of abemaciclib plus endocrine therapy should be in a postmenopausal state prior to therapy.

Verzenios as a single agent

The recommended dose of abemaciclib is 200 mg twice daily.

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

Dose modifications of Vezenios to manage adverse drug reactions can be made by dose interruption, reduction, or discontinuation. Dose reduction can be made to 150 mg/twice daily, 100 mg/twice daily, and 50 mg/twice daily according to guidelines in the SmPC, section 4.2.

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

For an overview of the clinical development programme, please refer to the tabular overview of clinical studies, section 3.3.

The applicant received Scientific Advice from the CHMP on 20 March 2014 and 24 September 2015. Scientific Advice pertained to quality, and clinical aspects of the dossier.

2.4. General comments on compliance with GMP, GLP, GCP

GMP: All relevant sites have valid manufacturing authorisations or valid GMP certificates as appropriate.

The applicant states that all clinical trials included in the MAA for abemaciclib were conducted in accordance with the ICH Good Clinical Practices (GCP) Guideline E6.

All pivotal non-clinical safety pharmacology and toxicology studies were conducted in accordance with GLP.

2.5. Type of application and other comments on the submitted dossier

- Legal basis – article 8(3) of Directive 2001/83/EC, new active substance
- Accelerated procedure - NA
- Conditional approval – NA
- Exceptional circumstances - NA
- Biosimilar application - NA
- 1 year data exclusivity - NA
- Significance of paediatric studies

Class Waiver Decision Number CW/1/2011

2.6. Quality aspects

2.6.1. Introduction

The finished product is presented as film-coated tablets containing 50 mg, 100 mg or 150 mg of abemaciclib as the active substance. Although the applicant also developed 200 mg tablets, these were withdrawn during the evaluation procedure due to the removal of the monotherapy.

Other ingredients are:

Tablet core: croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, colloidal hydrated silica, sodium stearyl fumarate;

Film coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172) [50 mg, and 150 mg tablets only], iron oxide red (E172) [50 mg tablets only].

The product is available in PCTFE/PE/PVC blisters sealed with an aluminium foil or aluminium/ aluminium perforated unit dose blisters as described in section 6.5 of the SmPC.

2.6.1. Active Substance

General information

The chemical name of abemaciclib is 2-pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1H-benzimidazol-6-yl]- corresponding to the molecular formula $C_{27}H_{32}F_2N_8$. It has a molecular weight of 506.59 and the following structure:

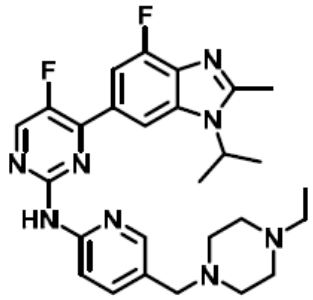


Figure 1: active substance structure

The structure of abemaciclib has been confirmed using different methods (mass spectroscopy, FTIR, ^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR, single crystal X-ray diffraction, UV and elemental analysis). All chemical, physical and spectroscopic data are in accordance with the structure.

Abemaciclib contains no chiral centres. This structural feature is consistent with the observation that this molecule is optically inactive. Polymorphism has been observed for abemaciclib.The crystal forms have been thoroughly characterized (physically and chemically) by X-ray powder diffraction, solid-state C NMR spectroscopy, solution-state H NMR spectroscopy, polarized light microscopy, thermal analysis and moisture sorption analysis. The thermodynamically most stable neat polymorph, Form III, was chosen for development. The current manufacturing (crystallization) process delivers Form III in highly crystalline and phase pure form.

Abemaciclib Form III is a practically white to yellow non-hygroscopic powder, practically insoluble in water and sparingly soluble in ethanol. The solubility is pH dependent . and it is a tri-basic substance. The particle size has been identified as a critical quality attribute (CQA).

Manufacture, characterisation and process controls

Abemaciclib is synthesized by a convergent multiple step synthesis using commerciallyavailable well defined GMP starting materials with acceptable specifications. Abemaciclib is isolated after controlled crystallization to produce Form III and milled to produce the required particle size distribution. The synthesis and the proposed starting materials are accepted as concluded in Scientific Advice.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DOE) studies. Robustness of unit operations, process parameters and controls were evaluated against the CQAs of the active substance (namely identity, potency, purity, particle size) ultimately linking them to the CQAs of the finished product (identification, description, potency, purity, content uniformity, release profile).

All steps in the synthesis are considered critical. Critical process parameters (CPPs) and their proven acceptable ranges (PARs) have been discussed and included in the process description. Design spaces have been claimed for all steps of the synthesis as part of the manufacturing process control strategy. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support these.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials, isolated intermediates and reagents have been presented.. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. A comprehensive evaluation of the actual and potential impurities that could be introduced via the raw material, starting materials, or intermediates, or that could be formed as by-products in the synthesis, or degradation products upon storage of the abemaciclib has been conducted. Stress testing studies were also conducted in order to understand the degradation and to identify potential impurities. Spiking studies were performed to demonstrate rejection of impurities during the synthesis. Overall, a good understanding of the source and fate of impurities in the process was demonstrated.

In addition, a genotoxic impurity assessment was performed using a combination of in silico toxicity predictions, visual alerts, external databases and *in vitro* assessments. All starting materials, intermediates, reagents, as well as potential impurities and degradation products were taken into account for this. A detailed explanation of the origin, fate, purge, and control of these potentially genotoxic impurities was provided. The overall control strategy based on the proposed specifications for the selected starting materials, intermediates and active substance specifications is satisfactory. As a result of this assessment, only one genotoxic impurity is routinely controlled in the active substance specification. This is acceptable.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in linear low density polyethylene (LLDPE) primary liner The liners may be placed in an appropriate container for shipping and handling. The materials of construction for the primary packaging component (that is, LLDPE liner) comply with the European Regulation 10/2011/EC, as amended, on plastic materials and articles intended to come into contact with food and also meet the testing compliance requirements of Ph. Eur. (Section 3.1.3, Polyolefins). Specifications for LDPE liner have been provided.

Specification

The active substance specification includes tests for description (visual), identity (IR/Raman), crystal form (X-ray powder diffraction), assay (HPLC), impurities (HPLC), residual solvents(GC,(HPLC)-, palladium (ICP-OES), particle size (laser light scattering), water (KF) and residue on ignition (Ph. Eur.).

This specification is based on the active substance CQAs: identity, potency, purity and particle size.

Palladium will be routinely controlled in the active substance. Particle size is a critical material attribute which can affect the active substance release from the dosage form and its specification limit has been justified. The polymorphic form is controlled by X-ray diffraction. The potential toxicity of abemaciclib impurities were evaluated as part of toxicology studies. However, given the projected dose, there are no specified impurities in the abemaciclib active substance above the ICH qualification threshold.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

A specification for the identified genotoxic impurity has been included. The limit is based on the toxicologically acceptable levels of the impurity at the projected dose. Solvents used in the process are controlled based on the requirements of ICH Q3C (R5) guideline or toxicologically justified. The omission of testing of elemental impurities, loss on drying and microbial purity has been satisfactorily addressed.

An elemental impurities risk assessment was conducted on abemaciclib following the principles outlined in ICH Q3D. Absence of microbial purity test has been justified

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented.

Batch analysis data from multiple batches of the active substance are provided.. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three batches of active substance manufactured at commercial scale by a process representative of the commercial process stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. These batches were packed in a pack equivalent of the commercial container The following parameters were tested: description, package characteristics, identity, assay, impurities, crystal form, and water content. Particle size distribution and surface area were also monitored The analytical methods used were generally the same as for release and werestability indicatingSamples were stored under both long term (up to 36 months) and accelerated conditions (6 months). These batches were tested for physical appearance, package characteristics, assay, impurities and crystal form. One batch was also tested for water content and particle size distributionThe active substance was shown to be stable.

All tested parameters remained within the specification and no trends were observed. No increase in impurities or loss of potency was observed and there was no change in physical properties throughout the duration of these studies.

Stress testing studies were also conducted in order to gain an understanding of abemaciclib degradation chemistry. Active substance in solid state was exposed to heat/humidity and light (as per ICH Q1B). Active substance in solution and suspension was exposed to a wide range of pH conditions at elevated temperatures, light, and oxidative conditions. Samples were assayed for abemaciclib content and impurities. Abemaciclib active substance in solid state did not exhibit any detectable degradation under the stress conditions of heat and humidity during the period tested. These results conclude that abemaciclib would be chemically stable when stored at ambient temperature and humidity. In addition, the photostability study showed no significant degradation in solid state samples exposed to simulated sunlight. These results indicate that abemaciclib would also be stable when the active substance is exposed to normal ambient lighting conditions.

Solutions of abemaciclib did not exhibit significant degradation across the pH range indicating that abemaciclib is not susceptible to hydrolysis. Solutions of abemaciclib in oxidative conditions underwent significant degradation, indicating that abemaciclib is susceptible to oxidative conditions in solution. The abemaciclib solutions containing trace metals did not undergo any degradation indicating that abemaciclib is not susceptible

to trace metal catalysed degradation. Significant degradation of abemaciclib was observed in all of the light-exposed solutions. The rate of photodegradation was pH dependent with the slowest photodegradation occurring at low pH.

The conclusion from the long-term, accelerated and stress degradation stability studies is that abemaciclib active substance would be chemically stable when stored at ambient temperature and humidity. The results also indicate that abemaciclib would be stable when the active substance is exposed to normal ambient lighting conditions. Therefore, the stability results justify the proposed retest period of 36 months in the proposed container without any special storage condition.

2.6.2. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product consists of oval immediate release film-coated tablets containing 50 mg, 100 mg or 150 mg of abemaciclib as active substance. As mentioned above, tablets containing 200 mg were also developed but were withdrawn by the applicant during the evaluation procedure. The dose strengths are differentiated by size, weight, debossment, and colour as depicted in Table 2.

Table 1. Description of the four dosage strengths of abemaciclib tablets.

Tablet strength (mg)	Description	Tablet Tooling Dimensions (mm)	Coated Tablet Weight (mg)
50	Modified oval beige tablet with “Lilly” debossed on one side and “50” on the other	5.2 × 9.5	144.2
100	Modified oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other	6.6 × 12.0	291.2
150	Modified oval yellow tablet with “Lilly” debossed on one side and “150” on the other	7.5 × 13.7	432.6

As indicated above, several crystalline forms of abemaciclib free base were observed during a comprehensive polymorph screening. Crystalline Form III is non-hygroscopic and is thermo-dynamically more stable than the other neat crystal forms, solvates and hydrates and was chosen for commercialization. The crystalline Form III of abemaciclib was used in all the clinical studies. Potential for phase transformation of abemaciclibwas evaluated during formulation development and ruled out.Abemaciclib crystalline Form III is highly soluble; the highest dose strength (200 mg) is soluble in less than 250 mL across the pH range 1 to 6.8. *In vitro* studies indicated that abemaciclib has moderate permeability. Therefore, abemaciclib was considered by the applicant a Biopharmaceutics Classification System (BCS) 3 molecule. *In silico* modeling suggested that the absorption of abemaciclib is not solubility/dissolution limited and is independent of particle size over a wide range.Nonetheless, an acceptance criterion for particle size was set using the x90 parameter to mitigate any residual risk to absorption. In addition, pharmacokinetic analysis of data from studies showed that the

absorption of abemaciclib is not formulation dependent (not solubility/dissolution-limited) and is independent of active substance particle size within the sizes that were used in the clinical studies.

All excipients are compendial and comply with Ph. Eur., except the colour mixtures which are composed of compendial ingredients, and Iron Oxide Yellow and Iron Oxide Red which comply with Commission Regulations (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The excipient levels chosen for the finished product are within typical ranges for solid oral dosage forms. The list of excipients is included in section 6.1 of the SmPC. and comprise microcrystalline cellulose (diluent), lactose monohydrate (diluent), croscarmellose sodium (disintegrant), silica colloidal hydrated (glidant), sodium stearyl fumarate (lubricant), polyvinyl alcohol (film-forming polymer), titanium dioxide (pigment/opacifier), macrogol (plasticizer/detackifier), talc (detackifier), and iron oxides (pigments).

Additional studies demonstrating the excipient selection and robustness for the levels of the selected excipients and their material attributes that could have impact on drug product CQAs have been presented.

In addition, the applicant discussed the functionality related characteristics of the active substance and excipients that may have an impact on the finished product manufacturability and provided details how the potential variability in these are eventually managed within the control strategy. In this regard, additional tests for relevant excipients have been presented.Based on the development studies presented the proposed specifications are considered sufficient for the continuous manufacturing process.

The goal of the pharmaceutical development efforts was directed to the production of a stable, bioavailable dosage form with consistent product performance attributes throughout its shelf life. Quality by Design (QbD) principles including risk assessments were used to ensure all desired quality attributes were addressed in the commercial abemaciclib tablets.

The formulation development activities, including the selection of excipients, their levels, and drug concentration were based on development experiments as well as previous experiences with similar materials.

To support Phase 1 and non-pivotal Phase 2 clinical studies, a drug-in-capsule formulation (C1 formulation) was developed. A formulated capsule (C2 formulation) was subsequentlty developed providing dose strengths ranging from 50 to 200 mg. Changes to the C2 formulation and process were made to improve manufacturing robustness, specifically to improve flow of the final blend and to provide better filled capsule weight control. This led to the C3 capsule formulation and process in which the active substance concentration was decreased . The C3 capsule formulation and process were used to manufacture all pivotal clinical study supplies.A tablet dosage form (T1, the proposed commercial formulation) was developed to minimize the size and the number of dosage units the patient would be required to take relative to the capsule dosage form To achieve these objectives, it was essential to maximize the active substance concentration in the formulation while maintaining acceptable CQAs. Thus, the tablet formulationutilizes a proportionally similar formulation to provide 50-, 100-, 150-, and 200-mg strengths by varying tablet weight and size. Each of the materials in the unit formula was selected to address the risks associated with identified factors. Development studies demonstrated that thechosen active substance concentration resulted in robust product and process performance.An initial formulation risk assessment was completed to assess the potential impact of material characteristics on finished product CQAs: description, identification, potency, purity, content uniformity, and release. No high risks were identified. This initial risk assessment was used to focus development on those areas with the potential of negatively impacting a finished product CQA. All of the medium risk items were investigated during development to provide a better understanding of their potential impact to product performance and develop an appropriate control strategy if needed.

Abemaciclib tablets are manufactured via a continuous direct compression process. Commercial formulation development commenced with studies to help inform the initial process risk assessment and assess the impact on drug product CQAs. The goal of these was to evaluate the robustness of the formulation. The results demonstrated the robustness of the formulation.

A bioequivalence study comparing the abemaciclib tablet formulations (50 mg and 150 mg) to the C3 capsule was performed. The 50 mg C3 capsule used in pivotal clinical trials was determined to be bioequivalent to the 50 mg and 150 mg T1 tablets (I3Y-MC-JPCC). The T1 tablet formulation and process used to manufacture the bioequivalence study batches are identical to those used to manufacture the tablet primary stability batches and are the intended commercial formulation and process.

A biowaiver for the 100 mg and 200 mg tablets was requested in line with the CHMP guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The 150 mg strength tablet was chosen as the reference because it is the highest strength tablet in the bioequivalence study. All tablet strength batches were manufactured at a scale that is at least 100,000 units or 1/10th the intended commercial scale (whichever is larger) and utilized the intended commercial manufacturing process. The results indicated that the dissolution characteristics of the finished product are not dependent on the product strength.

The choice of the dissolution method proposed for quality control (QC) has been thoroughly explained and justified. The dissolution method development was conducted with a goal of identifying method conditions that allowed complete recovery of the drug from the tablet while maintaining an appropriate degree of discrimination. In an attempt to obtain discriminating method conditions, different media additives, such as salts and surfactants, were evaluated. Based on the results obtained, the medium for the tablet QC dissolution method was selected, since this method is as discriminating as any of the methods that have shown adequate recovery. The selected media is commonly applied for highly soluble immediate release drug products and represents the dissolution of the finished product in the gastric pH environment. This method has been applied as the clinical trial material control method throughout the development of the tablets.

The use of the selected media for control of the commercial drug product is considered justified.

The manufacturing process development followed Quality by Design (QbD) principles. As indicated above, a continuous direct compression manufacturing process was selected for the manufacture of the commercial tablets. The manufacturing process consists of a pre-blend, loss in weight feeding of the pre-blend and other individual components, continuous powder mixing and tablet compression. Core tablets manufactured from this continuous process are then film-coated in a traditional batch process.

Each loss in weight (LIW) feeder uses active process control where process parameters (for example, screw speed) are automatically adjusted in response to common-cause and special-cause variability in order to maintain its actual mass flow rate near its set point. In addition to the local feeder controls, the feeding operation also has a system level control which makes all the feeders work together to ensure the unit formula is fed.

Process parameters were assessed using a Failure Mode, Effects, and Criticality Analysis (FMECA) risk assessment tool based on internal experience, first principles understanding, published literature and/or input from subject matter experts. Parameters ranked as medium or high risk were studied further and discussed.Site transfers during development and to commercial site have been adequately described. The results from this study were used to establish PARs as well as material attribute ranges. These are supported by the development data and controls in place. During the evaluation, the applicant confirmed that the process will be run at target parameters and no design space is claimed.

System modeling was completed to determine the continuous manufacturing system dynamics (for example, mixing capacity and particle residence time distribution (RTD), amplitude of the deviation in the feeding of one component and duration of the deviation). The Applicant has adequately described the investigations led to determine product RTD within the system. He has also explained how the limits established for all the feeders combined with the allowable mass flow rates and the mixer filtering capacity, are capable of dissipating any perturbation during process run and monitoring the state of control of the feeding operation.

In addition, in order to ensure the state of control of the process, the Applicant has developed a proactive control strategy and uses different elements to monitor and control the process performance and product quality. The data collected from the monitoring strategy are used as part of the control strategy to ensure that core tablet collection only occurs when all of the product collection criteria are met. RTD knowledge was used to define the amount of material that must be segregated due to the degree of intermixing that can occur from the point of detection to the point of segregation. This was defined such that all potential non-conforming material is removed from the process with high confidence.

The control strategy for each step of the continuous manufacturing has been properly detailed in terms of controls (for each step, for each equipment and control loops linked), alarms and material traceability.

A feed frame near infrared (FF NIR) method was developed to provide a prediction of the active substance concentration in the powder blend at the tablet press feed frame. The development followed a science and risk based approach, including risk assessments and design of experiment (DOE) studies to determine which variables may impact the NIR measurement. The description of the method is in line with Ph. Eur. monograph 2.2.40 and CHMP Note for guidance “Guideline on the use of Near Infrared Spectroscopy by the Pharmaceutical industry and the data requirements for new submissions and variations” (EMEA/CHMP/CVMP/QWP/17760/2009 Rev2). Details on the NIR instrument, software and fiber optic probe are provided, along with development and calibration information have been provided. Validation of the chemometric models has also been conducted and procedures for life-cycle maintenance have been presented in line with the CHMP guideline.

The primary packaging is PCTFE/PE/PVC blisters sealed with an aluminium foil or aluminium/aluminium perforated unit dose blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: pre-blending, feeding of the raw materials, continuous mixing and direct compression, and film-coating. Core tablets manufactured from this continuous process are then coated in a traditional batch tablet coating process.

In-process hold times have been defined and validated.

The batch formula has been adequately justified.As described above, the PAT applications are used for active substance concentration prediction in the in-line tablet press feed frame.

The bulk tablets are packaged in a monolayer low density polyethylene (LDPE) primary liner which contains no additives. The LDPE liner is placed in a secondary laminated foil liner. Each liner is independently cable tied or equivalent. The liners may be placed in an appropriate container such as a corrugated container, fiber drum, polyethylene drum, or metal drum for shipping and handling. It is stated that the materials of construction for the primary packaging component (that is, LDPE liner) comply with the European Regulation 10/2011/EC, as

amended, on plastic materials and articles intended to come into contact with food and also meet the testing compliance requirements of the European Pharmacopoeia (Section 3.1.3, Polyolefins).

Process validation data from three consecutive batches for each strength from various batch sizes, including the maximum initial commercial batch size for each strength have been provided. All results are well within acceptance criteria. The validation was comprehensive and comprised relevant parameters and acceptance criteria and the results indicate that the manufacturing process is under control and is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identity (IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (RTRT/HPLC), dissolution (UV), dye-identity (chemical).

The product specifications cover appropriate parameters for this dosage form.

The applicant's batch release strategy comprises real time release testing (RTRT) for content uniformity and traditional batch release strategy for other finished product CQAs.

UDU will be controlled by RTRT and it will comply if tested by HPLC. The HPLC will not routinely be performed. It will only be conducted as part of the NIR method model monitoring and maintenance strategy in batches which have been prospectively identified. Comparative results for process validation commercial scale batches usingthe NIR control strategy, plus a stratified sampling of tablets tested with the regulatory release method (HPLC, Ph. Eur. 2.9.40), were provided to support this. In addition, the Applicant proposes to continue parallel testing in order to ensure robustness of the system during the first year of commercial production on at least one batch per manufacturing campaign, and after at a minimum of not less than one batch annually.

The finished product batch analysis data together with risk assessment conducted in line with ICH Q3D supports the conclusion to not perform routine analysis of elemental impurities in the finished product.

Justification for not including test for moisture, microbial testing and crystal form were also provided based on the data obtained in the stability studies.The finished product is manufactured using a dry direct compression continuous manufacturing process.

One batch per strength of finished product per year is analyzed at release for microbiological purity. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented.

In-house analytical procedures are well described and validated in agreement with ICH guidelines and regional guidelines (i.e. NIR).

Batch analysis data for three commercial scale batches of each strength manufactured for commercial distribution at the commercial manufacturing site are provided(in total 12 batches). All batches comply with specification and confirm consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Batch data for three technical transfer batches (one batch of each strength), 12 primary stability batches (three batches of each strength) manufactured at the lower commercial scale using the commercial process, and

supporting batch data for the clinical trial capsule formulation were also provided. All batches complied with the specification.

Stability of the product

Stability data from three production scale batches of finished product of each strength stored for up to 12 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches are representative of the proposed commercial manufacturing site, processed at target process conditions.The batches of were packed in the primary packaging proposed for marketing.

Samples were tested for description (visual), package characteristics (visual), assay (HPLC), degradation products (HPLC), dissolution, water activity, crystal form (XRPD USP), TAMC, TYMC and specified organisms (*E. coli* and *Salmonella*) (Ph. Eur.). The analytical procedures used are stability indicating.

A matrixing design is used with a “one third reduction” on the 3-, 6-, 9-, and 18-month time points for three batches of each strength whereas all batches are tested at 12, 24, and 36 months.

No significant change or trends are observed up to 12 months and all results complied with the specification. No degradation products were observed above the 0.05% reporting threshold up to 12 months.

Supporting stability data from two clinical trial batches of abemaciclib tablets (50 and 150 mg) manufactured by a process representative of the commercial process were presented in an alternative packaging (container not claimed for marketing) and placed on stability at 30ºC/65% RH and at 40ºC/75% RH. Stability data are available up to 12 months for long-term storage and for up to 6 months accelerated storage conditions. No significant physical or chemical changes have been observed for the product, and these data further support a 24 month shelf-life for the abemaciclib commercial tablets.

Thermal/humidity stress testing was also conducted in order to gain understanding of degradation chemistry and to help identify potential degradation of abemaciclib tablets. Open-dish thermal/humidity stress stability studies were performed on one batch of each tablet strength manufactured by a process representative of the commercial processshowing no degradationAt levated temperatures a small total degradation increase was identified.

A photostability study was performed on one batch of each tablet strength in line with ICH Q1B. It showed no significant change in chemical or physical stability of the tablets as a result of the direct exposure to simulated sunlight conditions. Therefore, the finished product is considered photo stable.

Stability data of the bulk tablet have been provided at 5°C, 30°C/75% RH and 40°C/75% RH for the primary stability batches for each tablet strength. All the results in terms of assay, degradation products, description, package characteristics water activity, dissolution, crystal form,microbial quality complied with the acceptance criteria. Based on bulk hold studies for tablets a storage period of 18 months can be acceptable under the storage conditions of 5 to 30°C. Conditions of shipment have also defined, i.e. temperature should not exceed 30°C.

Based on available stability data, the proposed shelf-life of two years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.6.3. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Both developments for the active substance and finished product have followed QbD principles (risk assessments, design of experiments, establishment of ranges for process parameters, etc.) and detailed information has been provided. Design spaces have been claimed for the manufacturing process of the active substance. The tablets are manufactured via continuous mixing and direct compression. The applicant has conducted extensive studies to define the formulation and manufacturing process. An important knowledge of the product/process was gained through a data-rich environment which enables a performance based approach with focus on control of unit operation outputs. A proactive control strategy which gives the opportunity to react to perturbations (PAT tools, integrated controls and close process monitoring-forward control loops, real time handling of disturbances, segregation points to divert non-conforming material) has been established. The finished product specification comprises RTRT for content uniformity, and traditional batch release strategy for other finished product CQAs. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.6.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.7. Non-clinical aspects

2.7.1. Pharmacology

The active substance of Verzenios is abemaciclib. It is a small molecular weight molecule with the chemical formula C27H32F2N8 and the molecular weight of 506.59g/mol.

Primary pharmacodynamic studies

The pharmacological cellular mechanism of abemaciclib involves the inhibition of protein kinase activated cell proliferation in the G1 phase of the cell cycle.

The molecular mechanism of action of abemaciclib is based on the ATP-competitive inhibitory or preventive binding to human Cyclin dependent kinases 4 and 6 (CDK4 and CDK6), thereby reducing the probability of their binding to Cyclin D1 and the subsequent CDK4/CDK6-dependent phosphorylation of the retinoblastoma protein (p-Rb; evaluated on serine sites 780, 807, or 811).

The molecular specificity of abemaciclib for CDK4 and CDK6 was estimated using cell-free kinase assays (IC_{50}<10nM, see table below). The *in-vitro* cellular effect concentration for abemaciclib was measured in cell inhibition assays, giving an IC_{50} range between 210 and 450nM depending on cell line (e.g. A549 cells, Colo205 cells). The IC_{50} concentrations to alter p-Rb expression were between 151 and 180nM. Abemaciclib is known to have a number of human relevant metabolites (M1, M2, M18, M20, M21 and M22) whereof some (M2, M18, M20) also have similar levels of molecular affinity for the target molecules (see table below) and M2 and M20 are at >10% in humans.

Compound	CDK4/Cyclin D1 affinity data	CDK6/Cyclin D1 affinity data
Abemaciclib	IC_{50} 2.0nM IC_{50} 1.6nM	IC_{50} 9.9nM IC_{50} 2.0nM
Metabolite M2	IC_{50} 1.2nM	IC_{50} 1.3nM
Metabolite M18	IC_{50} 1.5nM	IC_{50} 2.7nM
Metabolite M20	IC_{50} 1.5nM	IC_{50} 1.9nM

The effective concentrations of abemaciclib and its metabolites differed in some cases between cancer cell lines and depending on endpoint (e.g. molecular biomarker express, cell inhibition). The Cell inhibitory IC_{50} difference between abemaciclib and its primary metabolites can range between 0.3x and 1.1x (M2) and between 0.6x and 1.4x (M20) between different breast cancer cell lines. For M18, there was an up to 11.5x margin for in effective concentration regarding changes in biomarker expression between cell lines. Overall, while abemaciclib itself seems relatively similar in its impact on different biochemical and in-vitro test systems, its metabolites seem to demonstrate a greater effect variation in in-vitro test systems. Reduced Rb-expression allows for abemaciclib resistance generation in cancer cell lines.

In a set of xenograft rodent model animals (based on injections of cancer cell lines or tumour fragment xenografts into the hind leg or back of the animals), abemaciclib was weakly to moderately effective as a treatment around 40-50 mg/kg (mostly stable disease to partial response, with tumour growth reduction but not tumour regression) and more clearly effective between 75-90 mg/kg (generating partial to complete response with tumour regression in some cases). One orthotopic xenograft study with glioblastoma cells showed that abemaciclib can be effective in neural cells. Whether a damaged blood brain barrier is a prerequisite is unknown.

Secondary pharmacodynamic studies

While the applicant has not provided any dedicated secondary pharmacodynamics studies, data on a set of kinases is present as *in-vitro* primary pharmacodynamics data. Out of the kinases screened, abemaciclib had a moderate inhibitory effect on a set of eight kinases at 6nM ≤ IC_{50} < 300nM (IC_{50} ranking PIM1 < HIPK2 < CDK9/Cyclin T1 < DYRK2 < PIM2 < CK2 < GSK3b < CDK5/P35). The PIM1 kinase has IC_{50} of 6nM, i.e. one the same level as CDK4 and CDK6, and CDK9 and HIPK2 have IC_{50}s of ≤~33nM. Follow up studies on CDK9 downstream targets p-CTD and MCL1 indicate that any potential binding CDK9 does not seem to have any downstream effects *in-vitro*. The inclusion of an additional receptor interaction study spanning 23 receptor and transporter proteins, it was found that the H2 and M2 receptors were the most potent binding targets with IC_{50} at 852 and 913nM respectively. This indicates a weak inhibition potential (i.e. IC_{50} 300-1000nM) and is above the clinical Cmax (123ng/mL, which gives a total concentration of 242.79nM and a free unbound fraction concentration between 7.28nM and 12.14nM at 95-97% plasma protein binding).

Safety pharmacology programme

Abemaciclib demonstrated a statistically significant inhibition at 1.65µM (-33.7%) in a hERG assay giving an IC_{50}>1.65uM (no higher concentrations were tested due to solubility issues). Based on a reported human Cmax of 123ng/mL, this gives a conservative estimated concentration of 242.8nM and a free concentration (at 95-97% plasma protein bound) of abemaciclib in humans between 7.3nM and 12.1nM and a hERG/Cmax ratio at 95% protein binding of 136. The main metabolite (M2, M18 and M20) hERG affinities were weaker (>10uM) than the parent compound. The standard core *in-vivo* Safety pharmacology (CNS, cardiovascular and respiration) studies have been conducted in rat (CNS, respiratory) and dog (cardiovascular). All studies used single-dose oral gavage and were GLP. Overall, no test article linked mortality or adverse clinical signs were observed with the exception in the dog study where one max-dose (10mg/kg) animal (out of eight) manifested post-dose paroxysmal ventricular tachycardia. There was also minor but statistically significant decrease (~1-3%) in the QT interval was seen at 1 and 10mg/kg. No similar findings were reported from the clinical safety data. The cause of the ventricular tachycardia remains unclear but is suggested that it is likely due to irritation originating from the insertion site of the left ventricular pressure transducer and/or positive ECG electrode.

Pharmacodynamic drug interactions

Treatment of xenograft mouse models with combinations of abemaciclib (dose range 50-75mg/kg, oral gavage) and fulvestrant (5mg/kg) alternatively tamoxifen (0.1mg/kg) did potentiate the abemaciclib effect in the breast cancer relevant xenograft mouse models (although the extent of the effects were xenograft specific). There are some indications that the combination treatments may generate a more durable growth inhibition in the post-dose period.

Pharmacokinetics

Method validation: Plasma samples from GLP repeat-dose toxicity studies in rats and dogs were analysed for abemaciclib and its main metabolites in humans LSN2839567 (M2), LSN3106726 (M20) and LSN3106729 (M18) using validated LC-MS/MS methods. In the pharmacokinetic distribution, metabolism and elimination studies, 14C-abemaciclib was used together with liquid scintillation spectrometry. A single 14C label was placed on the carbon bearing the methyl substituent of the benzimidazole group. The radiochemical purity was 98.8% and the largest individual impurity was <0.5%. Metabolite structural elucidation was carried out using LC-MS or LC-MS/MS. The bioanalytical methods are considered adequate.

Absorption: In single dose PK studies, abemaciclib was slowly absorbed and the oral bioavailability was estimated to be moderate to high in rats (~30-60%) and high (~84-85%) in dogs. In this respect, the rat is more similar to humans (45% bioavailability after single oral dose of 200mg). The Tmax in rats and dogs (6.67-8h) was similar to that in humans (8h). Dose-proportionality after single dose administration was evaluated in rats (one oral gavage and one 4h i.v. infusion study). With oral exposure, the Cmax increase was less than dose-proportional (AUC0-t could not be evaluated due to inadequate duration of plasma sampling). With i.v. exposure, the increase in AUC0-∞ was approximately dose proportional with similar clearance values across doses whereas the Cmax was less than dose-proportional. The volume of distribution and half-life increased as the dose increased, particularly at high doses of 40 mg/kg and 80 mg/kg.

Distribution: Tissue distribution in albino and pigmented rats was evaluated by quantitative whole body autoradiography (QWBA). After a single oral dose (10mg/kg), abemaciclib was strongly distributed to pigmented tissues/organs (eyes in particular), with a long elimination phase (half-life > 400 h). The top

distribution organs/tissues in rat besides the eyes were the skin (pigmented and non-pigmented), meninges, several glands (preputial gland, harderian gland, intra-orbital lacrimal gland, exorbital lacrimal gland, adrenal gland cortex and medulla), spleen, liver and kidneys.

Given the lack of eye or skin toxicity in the non-clinical studies (see Toxicology) or in the clinic (see Clinical part), the preferential distribution of abemaciclib to eye and skin does not appear to be associated with any obvious risk for toxicity in patients. An in vivo phototoxicity study in rats gave negative results (see Toxicology).

Reproductive organs (bulbo-urethral gland, prostate gland, epididymis, testes, ovaries and uterus) had also moderate to high levels of radioactivity. The distribution to the testes indicates that drug-derived radioactivity of abemaciclib crosses the blood-testis barrier to a certain extent. Radioactivity was also weak to moderate in blood-brain barrier protected tissues (cerebellum, cerebrum, medulla, and spinal cord) and very high in non-protected tissues (choroid plexus). Radioactivity in the CNS was detectable up to 12 to 24 hours post dosing.

Abemaciclib was highly bound to plasma proteins in rat, dog and human (~95-99%). The metabolites M2 and M20 had a somewhat lower binding (M2: ~83-92%; M20: ~76-94%) with the lowest bindings to dog plasma proteins (M2: 83%; M20: 76%). Distribution over the placenta or into milk has not been studied.

Metabolism:

In vitro; the in vitro metabolism of abemaciclib was evaluated in hepatocytes and liver microsomes of rat, dog and human. The metabolic turnover in hepatocytes was low in rat and dog when compared to human. Qualitatively, in vitro metabolism in hepatocytes was consistent among species and produced the same 4 four oxidative metabolites: LSN2878851 (M1), LSN2839567 (M2), LSN3106726 (M20) and a fourth metabolite whose structure has not been fully established.

In vivo; abemaciclib underwent extensive metabolism in vivo in rat, dog and human. The major component in plasma of all three species was unchanged abemaciclib. The most prominent (active and major) plasma metabolites in human were M20 and M2. Exposure to these metabolites was evaluated in rat and dog repeat-dose toxicity studies (see Toxicology section). All metabolites identified in human feces, the predominant elimination route for abemaciclib and its metabolites, were also detected in dog feces. The major elimination pathway, N-desethylation to form metabolite M2, was consistent in rat, dog, and human.

Excretion: Mass balance data was obtained from rats and male Beagle dogs. Overall, the results indicate that elimination pathways for abemaciclib in rats and dogs were similar (i.e. N-desethylation to form metabolite LSN2839567/M2); the majority of absorbed drug-related radioactivity being eliminated by metabolism via bile, or by direct secretion into faeces. A similar excretion profile has been observed in humans.

Pharmacokinetic drug interactions: For discussion, see the Pharmacokinetics section.

2.7.2. Toxicology

The toxicological profile of abemaciclib has been evaluated in agreement with recommendations in ICH S9. The performed studies comprise repeat-dose toxicity studies for up to 3 months in rats and dogs, in vitro and in vivo genotoxicity, embryo-foetal development toxicity in rats, and in vivo phototoxicity. In addition, two major human metabolites (M2, M20) were evaluated in a standard package of genotoxicity studies.

Rats and dogs were used for toxicity studies based on the expression of target and similarity of metabolism to humans. Based on demonstration of target-related findings, both species are considered to be pharmacologically relevant.

Single dose toxicity

No dedicated single-dose toxicity studies were conducted, which is acceptable. Rats tolerated a single dose of 300 mg/kg/bw in the in vivo micronucleus study.

Repeat dose toxicity

Mortality

In the 1-month rat study, two satellite rats administered 50 mg/kg/day were euthanized or died on Days 20 and 14, respectively. Clinical signs preceding death were decreased activity, dehydration, reduced appetite, soft or reduced feces, and decreased body weight. In the 3-month rat study, one satellite rat administered 30 mg/kg/day was found dead on Day 73, having lost 42 g during the last body weight collection interval. Intestinal toxicity (see further below) is considered to be the main cause of death in these rats.

In the 1-month dog study, one male and one female dog at 10 mg/kg/day were pre-terminally euthanized on Days 12 and 15, respectively, due to poor health condition. Clinical signs included decreased activity, tremor, suspected dehydration, thinness, weakness, liquid faeces and vomiting. Both dogs had lost weight, due to decreased food consumption. Intestinal lesions (villous/mucosal atrophy, cryptal necrosis, and haemorrhage) were the main cause of the deteriorating condition, with severe hematopoietic hypocellularity of the bone marrow contributing to the morbidity.

Clinical signs, body weight and food consumption

Rats treated at $\geq$ 30 mg/kg/day for 1 month showed salivation, wet fur, dried/flaking/red/scabbed skin, fur effects (thin, alopecia), prominent backbone, dehydration, decreased activity and hypersensitivity. At $\geq$ 10 mg/kg/day, food consumption, mean body weight and body weight gain were decreased. In the 3-month rat study, there were no clinical signs up to 30 mg/kg/day, although food consumption was decreased at 30 mg/kg/day and mean body weight and body weight gain were decreased at $\geq$ 3 mg/kg/day.

Dogs treated at 10 mg/kg/day for 1 month showed the same clinical signs as the preterminally euthanized dogs (see under Mortality). Soft/liquid faeces and decreased food consumption were observed at $\geq$ 1 mg/kg/day. Decreased body weight and body weight gain occurred mainly at 10 mg/kg/day. In the 3-month study, slightly decreased body weight and body weight gain were observed in females at $\geq$ 0.3 mg/kg/day, associated with lower food consumption and prominent backbone at > 1 mg/kg/day.

The majority of clinical signs, and effects on body weight in rats and dogs, are considered due to the intestinal lesions caused by abemaciclib administration (see below).

Effects on the small and large intestine

Minimal to moderate crypt hyperplasia, epithelial degeneration/atrophy and neutrophilic inflammation were observed in the small and large intestine of rats treated at $\geq$ 30 mg/kg/day for 1 month. These findings were associated with hematological effects: increased white blood cells, neutrophils and lymphocytes. Decreases in serum total protein, albumin, globulin and calcium at $\geq$ 10 mg/kg/day reflected loss via the intestinal wall. It can

be noted that in all sections and at all doses, the architecture of each respective intestinal segment was maintained, the epithelium was intact (absence of obvious erosion/ulceration of the mucosa), and active appropriate regeneration was occurring within the crypt (hyperplasia: crypt). Minimal to mild crypt hyperplasia was present in the duodenum of rats treated at ≥ 10 mg/kg/day for 3 months, with associated decreased serum total protein, albumin, globulin and calcium.

Dogs administered 10 mg/kg/day for 1 month showed minimal to marked villous/mucosal atrophy (duodenum, jejunum, ileum), minimal to moderate crypt hyperplasia (duodenum, jejunum, ileum, cecum, colon), minimal to slight crypt necrosis (jejunum, colon), slight subacute inflammation (ileum, cecum) and minimal to marked hemorrhage (duodenum, jejunum, ileum, colon). No intestinal effects were observed in the 3-month study, using doses up to 3 mg/kg/day.

Diarrhoea, nausea, vomiting, abdominal pain and decreased appetite are common adverse events in clinical trials with abeciclib. The proposed SmPC contains information concerning this risk in section 4.8.

Effects on the bone marrow and lymphoid system

In all rat and dog studies, bone marrow hypocellularity and lymphoid depletion in the thymus (associated with small thymus and decreased thymus weight) were observed, at doses ≥ 10 mg/kg/day (rat) and ≥ 0.3 mg/kg/day (dog). In rats, there was an additional finding in the thymus in form of medullary hypercellularity. Correlating hematological changes in rats and dogs were seen with decreases in myeloid: erythroid ratio (dog), reticulocyte count, red blood cell count, hemoglobin and haematocrit, as well as decreases in lymphocytes, neutrophils, monocytes, platelets and eosinophils. In the 3-month rat study, increased MCV, MCH and RDW were also observed, at ≥ 3 mg/kg/day. Rats treated at ≥ 10 mg/kg/day for 3 months showed decreased APTT, which may have been related to the bone marrow cytotoxicity.

At higher doses (≥ 30 mg/kg/day in rats, ≥ 3 mg/kg/day in dogs) decreased lymphoid follicles and germinal centers were seen in lymph nodes and the gut-associated lymphoid tissue (GALT). In rats, paracortical hypercellularity was noted in parallel with the decreased lymphoid cellularity in the B-cell areas. In dogs, there was decreased lymphoid cellularity affecting both follicular (B-cell) and paracortical (T-cell) areas.

Anemia and decreased white blood cells have been reported in clinical trials with abemaciclib. 'Severe infection secondary to neutropenia' is included as an important identified risk in the RMP. The proposed SmPC contains information and warnings concerning this risk in sections 4.2, 4.4 and 4.8. From a non-clinical perspective, no further action is considered necessary.

Effects on the male reproductive system

In rats treated at ≥ 10 mg/kg/day for 1 month, decreased testis weight and testicular degeneration/depletion of germ cells, associated with spermatid retention, were observed. Additional male reproductive organ findings included intratubular cellular debris in the epididymis and decreased epididymis weight, decreased prostate weight and prostate atrophy, and seminal vesicle atrophy. The testicular effects are considered due to the pharmacological effect of abemaciclib on dividing cells (mitotic spermatogonia and meiotic spermatocytes), resulting in abnormal spermatogenesis. The atrophy observed in the prostate gland and seminal vesicle is considered to be secondary to the testicular toxicity. In the 3-month rat study no male reproductive toxicity was observed, despite similar exposure at 10 mg/kg/day as in the 1-month study. The reason for this discrepancy is not clear.

In dogs, slight seminiferous tubule degeneration with minimal hypo/aspermatogenesis in the testis, and corresponding oligo/aspermia in the epididymis, was observed at ≥ 3 mg/kg/day in the 1-month study. These

effects became more pronounced in the 3-month study, where decreased testis weight correlating with minimal to severe seminiferous tubule degeneration/necrosis, and epididymal cellular debris, occurred at ≥ 0.3 mg/kg/day. Marked to severe oligo/aspermia was present at 3 mg/kg/day.

The LOAEL for testicular toxicity in dogs was below the intended clinical AUC exposure. Based on the observed testis toxicity, male fertility may be compromised by treatment with abemaciclib. This information is included in section 4.6 of the SmPC. From a non-clinical point of view, no further action is needed.

Effects on the kidney

Rats administered abemaciclib at > 30 mg/kg/day for 1 month showed minimal to slight vacuolation/degeneration of collecting ducts. Tubular basophilia was observed in males after recovery, suggesting regeneration. In the 3-month study, rats treated at 30 mg/kg/day showed mild glomerular changes, increased incidence of minimal to moderate tubular degeneration/regeneration, tubular pigmentation and minimal medullary necrosis. These findings were accompanied by increased urea and creatinine in males, as well as decreased urinary volume, increased urine specific gravity and lower pH in males. No renal effects were observed in dogs.

The clinical relevance of the renal effects in rats is uncertain. In clinical trials, abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters. There was no indication of renal dysfunction in patients. Information regarding the effect on serum creatinine is included in sections 4.5 and 4.8 of the SmPC. See further the Clinical Pharmacokinetics Assessment Report.

Effects on the lung

Abemaciclib caused macrophage accumulation in the lung of rats treated at ≥ 10 mg/kg/day for 1 month, and at ≥ 3 mg/kg/day for 3 months. At higher doses (30 mg/kg/day in the 1-month study, ≥ 10 mg/kg/day in the 3-month study) pulmonary inflammation was observed. The Applicant speculated that the inflammatory changes might be due to opportunistic infection, exacerbated by abemaciclib-related impairment of the immune system. This seems possible.

Increased frequency of infections was observed in patients treated with abemaciclib in clinical trials. ‘Serious infection secondary to neutropenia’ is included as an important potential risk in the RMP. From a non-clinical perspective, no further action is considered necessary.

Other effects

Adrenal gland microscopic changes (minimal to moderate cortical cytoplasmic eosinophila/decreased vacuolation) were observed in dogs treated at ≥ 1 mg/kg/day for 1 month and at ≥ 0.3 mg/kg/day for 3 months. Markedly increased serum cholesterol at the same dose levels appeared to be a related effect. At higher dose levels, the weight of the adrenal gland was significantly increased. Minimal to slight mononuclear cell infiltration was seen in the adrenal gland at ≥ 3 mg/kg/day in the 1-month study. In rats, increased cholesterol was observed at ≥ 10 mg/kg/day. The mechanism behind the observed effects on the adrenal gland and cholesterol levels is unclear; however, it is not considered to be an adverse effect and no significant changes in cholesterol have been observed in patients.

Some additional non-adverse findings included macrophage accumulation in the gall bladder of dogs treated at 3 mg/kg/day for 3 months; increased pigment deposition in the splenic red pulp of dogs treated at ≥ 1 mg/kg/day for 3 months; acinar cell vacuolation in the pancreas, and macrophage vacuolation in the spleen of rats at ≥ 30 mg/kg/day.

Mammary gland atrophy was observed in male rats at ≥ 10 mg/kg/day in the 1-month study. Since no similar change was present in female rats or in dogs the clinical relevance is uncertain. Myofiber degeneration was present at 50 mg/kg/day in rats treated for 1 month. Since this finding occurred at an exposure ~ 15-fold above human therapeutic AUC its clinical relevance is considered low.

Electrocardiography (ECG)

In the 4-week and 3-month dog toxicity studies, there were no treatment-related effects on morphology, heart rate, QT and QTc intervals.

Reversibility

Bone marrow hypocellularity was not reversible in rats. In dogs, there were persistent decreases in red blood cells, haemoglobin and haematocrit; however, reticulocytes increased at the end of the recovery period, indicating a regenerative response and correlating with microscopic hepatic extramedullary hematopoiesis noted in all recovery animals at 10 mg/kg/day. Testicular degeneration and intratubular cellular debris in the epididymis, associated with decreased testicular and epididymal weight did not show any recovery in rats. Possible compound-related seminiferous tubule degeneration with minimal hypo/aspermatogenesis and corresponding oligo/aspermia in the epididymis was observed in one recovery dog at 10 mg/kg/day. Since the spermatogenic cycle duration in rats and dogs is 48-53 days and ~8 weeks, respectively, the recovery periods of 4 weeks were not of sufficient duration to evaluate full recovery.

Genotoxicity

Abemaciclib was evaluated in a standard package of *in vitro* (mutation in bacteria, chromosome aberration) and *in vivo* (rat micronucleus) genotoxicity tests. The doses used in the micronucleus test were much higher than the doses used in the 28-day repeat dose toxicity studies. The results were negative and did not reveal any evidence of genotoxic potential of abemaciclib.

Carcinogenicity

In accordance with ICH S9, carcinogenicity studies with abemaciclib have not been conducted given the intended treatment of patients with advanced cancer. This is endorsed.

Reproduction Toxicity

The effects of abemaciclib on embryo-fetal development was evaluated in the rat, over a dose range of 1, 4 and 15 mg/kg/day. Decreased food consumption, body weight gain and body weight occurred at ≥ 4 mg/kg/day. Maternal performance was not affected by treatment. Decreased uterine and fetal weight was observed at ≥ 4 mg/kg/day. Increased fetal cardiovascular malformations and variations were observed at 15 mg/kg/day. Furthermore, tail malformations in two fetuses from different litters, an increased incidence of rib malformations (not statistically significant) and increased skeletal variations, were observed at 15 mg/kg/day. At 4 mg/kg/day there was a minor increase in cardiovascular malformations and variations, of the same type seen at 15 mg/kg/day. A relationship to treatment with abemaciclib cannot be excluded.

Exposure (AUC_{0-24}) at 4 mg/kg/day was 5250 ng x h/mL on GD 17, corresponding to a 1.5-fold margin to human clinical exposure at 400 mg/day. The NOAEL for maternal toxicity and embryo-fetal development was 1

mg/kg/day, corresponding to an AUC_{0-24} of 843 ng x h/mL on GD 17. This is 0.2-fold the clinical exposure at the maximum therapeutic dose (400 mg/day)

Based on these results abemaciclib is considered to be teratogenic in the rat, at clinically relevant exposure levels. Appropriate warnings and recommendations are given in section 4.6 of the SmPC.

The Applicant did not conduct any EFD study in rabbits. This is acceptable in accordance with the recommendations in ICH S9, stating that in cases where an EFD study is positive for embryofetal lethality or teratogenicity, a confirmatory study in a second species is usually not warranted.

No studies on fertility or prenatal and postnatal development were conducted. In accordance with ICH S9, the absence of these studies is acceptable.

Toxicokinetic data and interspecies comparison

Toxicokinetics and interspecies comparison

After daily oral gavage administration, mean exposures (C_{max} and AUC_{0-24h}) to abemaciclib generally increased proportionally to dose in rats and dogs. Slight accumulation (1.5 to 3-fold) was observed in both species. There was no clear gender difference. The mean AUC_{0-24h} exposure to abemaciclib in rats at the MTD in the 3-month study was 31050 ng·h/mL., corresponding to a 9-fold margin to human therapeutic exposure at 400 mg/day. The AUC multiples at the NOAEL (1-month study) and LOAEL (3-month study) compared to the clinical AUC were ~3-4-fold and 1-fold, respectively. In dogs, the mean AUC_{0-24h} exposure at the MTD in the 3-month study was 1565 ng·h/mL, which was 0.5-fold the human maximum exposure.

Local Tolerance

The local tolerance of abemaciclib following oral administration was evaluated in the repeat-dose toxicity studies. There were no effects indicating local irritancy in these studies. The potential for ocular and dermal irritation was assessed in the bovine corneal opacity and permeability (BCOP) *in vitro* test, and an *in vivo* dermal toxicity study in rats, respectively. The results indicate that abemaciclib is a non-irritant to eyes and skin.

Other toxicity studies

Metabolites

The two major human metabolites M2 and M20 were analysed in the 3-month rat and dog studies. In rats, exposure in terms of AUC_{0-24h} was higher than in humans. Thus M2 has been toxicologically qualified. The exposure to M20 was 22-fold less than that observed in humans. However, in excreta M20 and its downstream metabolite M21 were eliminated in dogs at similar levels (as % dose) to that in humans (see Pharmacokinetics). In accordance with ICH S9, toxicological qualification of human metabolites is not required for patients with advanced cancer.

M2 and M20 were evaluated for genotoxicity in bacterial mutation (Ames) and chromosome aberrations *in vitro* tests. Both metabolites were negative in the Ames test. The M2 and M20 studies were not in conformity with GLP but the applicant has provided a detailed description of formulation and stability which supports the validity of the studies. In the *in vitro* chromosomal aberration tests, M2 and M20 in the 3-hour assays with or without metabolic activation caused a significant increase in the number of cells with endoreduplication. According to the

Applicant, this could have been due to an effect on the mitotic process or disruption of the cell cycle. For the present application no follow-up studies are considered necessary; however, in case of a future application outside the scope of ICH S9 the Applicant is recommended to conduct additional experiments *in vitro* and/or *in vivo*, in line with the ICH S2R1 guideline on genotoxicity testing.

Phototoxicity

There was no evidence of cutaneous or ocular phototoxicity after a 3 day oral (gavage) administration of abemaciclib at doses up to 40 mg/kg/day in pigmented Long Evans rats, following a single exposure to UVR approximately 2 hours after the final dose administration.

2.7.3. Ecotoxicity / environmental risk assessment

Summary of main study results

The environmental risk assessment (ERA) for abemaciclib covers a full ERA phase I, IIA and IIB including PBT assessment and is only based on the parent compound and not any of the metabolites. Abemaciclib is slightly lipophilic with a log K_{OW} of 3.6 at pH7. The default Phase I surface water predicted environmental concentration (PEC_{SW}) was calculated to 2.0ug/L (based on Fpen = 1%). A refined Phase IIB PEC_{SW} calculation gives 0.033ug/L (see also Non-clinical discussion).

Abemaciclib is not readily biodegradable. It is a very persistent molecule in most environmental mediums, demonstrating very little chemical degradation in water (<10% hydrolysis at 50°C), a DT_{50} of a maximum of 744d in sediment (estimated for 12°C), a sludge DT_{50} of 107d (with weak to moderate primary biodegradation and almost no ultimate biodegradation) and sludge adsorption K_{dOC} > 10000L/kg, and a soil DT_{50} of up to 2629d with soil K_{fOC} between 242804 and 1947392L/kg. Abemaciclib seems to move relatively quickly into sediment from water (~91% after 14d).

The minimum NOEC in the standard aquatic toxicity package was 5.9ug/L (microalgae; P. subcapitata, 72h; mean yield endpoint), nominally triggering the toxicity classification (T<10ug/L) in a PBT assessment. Daphnids were almost as sensitive with a NOEC of 20ug/L. The lipid and growth corrected kinetic bioconcentration factor (BCF) in fish (Bluegill) was 289-383L/kg and as such below the trigger for bioaccumulation (2000L/kg) in PBT (see also Non-clinical discussion). As abemaciclib has a log K_{OW}>3, is resistant to hydrolysis and has high adsorption, a secondary poisoning discussion has been provided by the applicant (see also Non-clinical discussion). The organic content (OC) normalized (10%) NOEC for sediment-dweller toxicity in *C. riparius* was 780mg/kg. The lowest NOEC (OC2% normalized) was the NOEC 82mg/kg (pre-normalized NOEC 243mg/kg) for acute toxicity in earthworm (*E. fetida*). The most sensitive plant species was tomato, demonstrating phytotoxicity with an $NOEC_{OC2\%}$ of 322mg/kg (pre-normalized NOEC 108mg/kg). Abemaciclib did not demonstrate any potential for bacterial toxicity with NOECs between 970 and 1020mg/kg for sludge and soil microorganisms.

Table 1. ERA summary

Substance (INN / Invented Name): Abemaciclib			
CAS-number (if available): 1231929-97-7			
PBT screening	**Test protocol**	**Result**	**Conclusion**
Bioaccumulation potential- log K_{OW}	OECD123	3.6 at pH7	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{OW}	3.6 at pH7	Possible B
	BCF	289-383 < 2000 L/kg	not B
Persistence	DT50	*Whole sediment-water* DT_{50} = 366d at 12°C *Sediment* DT_{50} = 774d at 12°C *Water* DT_{50} = 5.3d *Soil* DT50 = 1096 to 2629d	vP
Toxicity	NOEC	5.9 ug/L < 10ug/L Possible male reprotoxicant (R in CMR)	T Based on dog studies (LOAEL 0.3mg/kg, no NOAEL, 3 month study).
PBT-statement :	While both highly persistent and toxic to microalgae and daphnia, the compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{SW}, default PEC_{SW}, refined	2 (Phase I) 0.033 (Phase IIB)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	Soil 1 Kfoc = 14854332 Soil 2 Kfoc = 242804 Soil 3 Kfoc = 1947392 Sludge1 Kdoc = 80598 Sludge2 Kdoc = 20035	Soil 1: RMN soil Soil 2: DU soil Soil 3: MSL soil The sludge values are based on 0.01mg/L active substance.
Inherent Biodegradability Test	OECD TG302A	<u>After 7d at 20°C:</u> $DT_{50,\ SLUDGE}$ = 85.6d Parent AR = 89.7% Total TP AR <10% Ult. biodegrad. = 0.02%	Sludge from Wareham WWTP. Preliminary study to OECD TG314B.
Ready Biodegradability Test	OECD TG314B	<u>After 28d at 20°C:</u> $DT_{50,\ SLUDGE}$ = 107d Total TP AR = 20.5% Parent AR = 78.1% Ult. biodegrad. < 0.1%	Sludge from Wareham WWTP
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	<u>Empirical 20°C</u> $DT_{50,WAT}$ = 2.7-2.8d $DT_{50,SED}$ = 21.9-407.7d $DT_{50,WHS}$ = 60.3-192.5d <u>Calculated 12°C</u> $DT_{50,WAT}$ = 5.1-5.3d $DT_{50,SED}$ = 42-774d $DT_{50,WHS}$ = 114-366d % shifting to sediment > 10% (~91% after 14d)	Not required if readily biodegradable

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition	OECD TG201	NOEC	5.9	ug/L	*P. subcapitata*

Test/*Species*		LOEC EC50	14 19		Mean yield most sensitive endpoint.
Daphnia sp. Acute Immobilisation Test	OECD TG202	NOEC LOEC EC50	5.6 11 >43	mg/L	Daphnia sp. immobilizatio n after 48h
Daphnia sp. Reproduction Test	OECD TG211	NOEC LOEC EC50	20 50 130	µg/L	Reproduction endpoint most sensitive
Fish, Acute Toxicity Test	OECD TG203	NOEC LOEC LC50	1.2 1.9 6.2	mg/L	*P. promelas 96h exposure*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC LOEC	75 170	µg/L	*P. promelas* The most sensitive endpoint was body mass and weight.
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC LOEC	1000 >1000	mg/L	Sludge from Wareham WWTP
Phase IIb Studies					
Bioaccumulation	OECD TG305	BCF_{SS}* BCF_K* BCF_{KGL}* BCF_{KL}* BCF_{KG}* $T_{1/2G}$	54-75 175-231 289-383 144-190 352-465 114-116	L/kg L/kg L/kg L/kg L/kg d	Fish: Bluegill Whole fish % lipids at d43: 6.8-9.7% Incomplete depuration in study.
Aerobic transformation in soil	OECD TG307	*Loam* DT50 $\%CO_2$ *Loamy sand* DT50 $\%CO_2$ *Sandy loam1* DT50 $\%CO_2$ *Sandy loam2* DT50 $\%CO_2$	 1155 0.079 1386 0.045 578 0.084 1155 0.071	 days % days % days % days %	No volatiles.
Soil Microorganisms: Nitrogen Transformation Test Carbon Transformation Test	OECD TG216 OECD TG217	NOEC LOEC %effect $NOEC_{OC2\%}$	485 970 1020	mg/kg dry weight	Soil: Loamy sand. OC: 0.95%
Terrestrial Plants, Growth Test/*Species*	OECD TG208	NOEC LOEC $NOEC_{OC2\%}$ Most sensitive species: Tomato	108 323 322	mg/kg dry weight	Tested plants: Oilseed rape Soybean Sunflower Tomato Wild oat Ryegrass
Earthworm, Acute Toxicity Tests	OECD TG207	NOEC LOEC $NOEC_{OC2\%}$	243 485 82	mg/kg dry weight	*E. fetida* Artificial soil. Effect on body weight gain.

Collembola, Reproduction Test	OECD TG232 ISO 11267	NOEC LOEC $NOEC_{OC2\%}$	970 >970 669	mg/kg dry weight	*F. candida*
Sediment dwelling organism	OEC TG218	NOEC $NOEC_{OC10}$ LOEC	140 780 410	mg/kg dry weight	*C. riparius*

* BCF stands for bioconcentration factor, BCF_{SS} is steady state BCF, BCF_K is kinetic BCF, BCF_{KGL} is lipid and growth corrected kinetic BCF based on whole fish total radioactivity, BCF_{KL} is lipid-normalized kinetic BCF, BCF_{KG} is growth-normalized kinetic BCF and $t_{1/2G}$ is growth-corrected half-life.

After Phase IIB refinement for PEC in all environmental compartments (i.e. surface water, ground water, sediment, sludge, sludge on soil), the applicant has provided a set of risk quotients/ratios (RQs) that are all below 1 (see below for PEC, PNEC and RQ values).

PEC*	PNEC organism	PNEC	RQ
Refined PEC_{SW} 0.0330 µg/L	Microalgae	0.59 ug/L	0.056x
Refined PEC_{GW} 0.0043 µg/L	Daphnia	2.0 ug/L	0.0022x
Refined PEC_{MO-STP} 0.520 µg/L	Sludge microorganisms	1000 000 ug/L	0.0000052x
Refined PEC_{MO-SW} 0.033 µg/L	Water microorganisms	1000 000 ug/L	0.0000003x
Refined PEC_{SED} 4.0mg/kg	Chironomid larvae	7.8 mg/kg**	0.51x
Refined PEC_{SOIL} 0.094 mg/kg	Earthworm	8.2 mg/kg	0.011x

* PEC_{SW} stands for surface water PEC, PEC_{GW} stands for ground water PEC, PEC_{MO-STP} stands for STP sewage sludge microorganism PEC, PEC_{MO-SW} stands for surface water microorganisms, PEC_{SED} stands for sediment PEC, and PEC $_{SOIL}$ stands for soil PEC. ** PNEC calculated with AF = 100.

In the fish bioconcentration study (OECD TG305), while the BCF (see ERA summary table) was calculated to be <2000L/kg and therefore unlikely to bioaccumulate, it can be noted that depurination was incomplete within the study boundary (uptake duration before steady state: 42d, an experimental depurination period of 60d). The length of the depurination was likely to short as the radioactivity of the whole body did not sink to initial exposure levels. The risk for secondary poisoning was assessed by the applicant, giving a $PEC_{oral,\ top\ predator}$ of 13ug/kg fish, a $LOAEL_{oral,\ mammal}$ of 12 mg/kg food (based on 0.3mg/kg 90d gavage exposure in dog) and a $PNEC_{oral}$ of 40ug/kg food (based on a food conversion factor CONV of 40). The PNEC was based on the dog LOAEL and an Assessment factor (AF) of 326.7 (the sum of uncertainty factors: LOAEL --> NOAEL 10x; 90d sub-chronic exposure to chronic exposure 3x; interspecies uncertainty 3.3x; Lab to field uncertainty 3.3x). The applicant argues that because dog is much more sensitive than the most sensitive NOAEL in a second species (10 mg/kg in rats), an uncertainty factor of 3.3x (instead of 10x) is considered appropriate to account for interspecies sensitivity. The logic underlying the interspecies argument is not clear but in both AF cases, the $PEC_{oral,\ top\ predator}$ is formally less than the $PNEC_{oral}$ (although with a very small margin for AF 30x). As such, and considering the additional uncertainty factors included (10x & 3x & 3.3x & 3.3x = ~327x), it is agreed that there is not sufficient evidence to classify abemaciclib as a secondary poisoning risk. That being said, the incomplete depuration with an elimination half-life of 115 days (tissue concentrations of 45 - 48% after 60 days) should be mentioned in the final assessment and EPAR as the incomplete depuration is an important information.

2.7.4. Discussion on non-clinical aspects

Pharmacology: The pharmacological data provide a molecular and cellular level of mechanism of action. The proof of principle for the therapeutic indication (breast cancer) is evaluated in traditional cancer animal models (i.e. mostly ectotopic cancer cell line/tumour fragment xenograft rodent models). This leaves the common

tumour development, drug efficacy and immunology-related uncertainties about microenvironment-tumour relations when using such models.

The Applicant considers the pharmacologically active metabolites to be equivalent to the parent compound based on biochemical affinity, but there is some additional variation in biological effects of these metabolites in various in-vitro test systems (indicating that the affinity values are not fully representative of biological similarity). Besides the target proteins, abemaciclib seems to target other enzymes such as PIM1 at clinically relevant concentrations. After follow-up question, the applicant provided further discussion on the pharmacodynamic role of PIM1 and refers to several studies (non-submitted) that seem to indicate that the inhibition of PIM1 helps in the intended therapy. So, while the data cannot be assessed for a definitive inclusion of PIM1 among the target proteins, this nominally indicates that PIM1 may be relevant for the pharmacodynamic effect.

There are some minor indications that combination treatment with fulvestrant alternatively tamoxifen may increase the potency of abemaciclib in breast cancer xenograft mouse models. Overall, there are no major issues about nonclinical pharmacology.

Pharmacokinetics: The non-clinical pharmacokinetic profile of abemaciclib is considered to have been adequately characterized. Rats and dogs were chosen by the Applicant as target species for the toxicology studies. Despite a few differences in metabolic pathways, these species showed qualitatively a similar metabolic profile as humans and are thus considered adequate for evaluation of the toxicity of abemaciclib.

Toxicology: The bone marrow, lymphoid tissues, male reproductive organs and intestines were identified as target organs in both rats and dogs. Additional target organs in rats were the kidney and lung, and in dog the adrenal glands. Regarding the renal effects in rat, this information has been included in the SmPC 5.3. In clinical trials, abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters. Moreover, information regarding the effect on serum creatinine is also is included in sections 4.5 and 4.8 of the SmPC. Because acute kidney injury was also reported in about 2% (consistent with GI adverse effects), it was decided that this should however be closely monitored within PSURs in the case of an approval. Intestinal crypt hyperplasia were observed in rat and dog repeat dose toxicity studies, but are considered to reflect a regenerative response.

The majority of effects are considered directly or indirectly related to the pharmacological inhibition of cell replication in tissues due to CDK4/6 inhibition. Toxicity occurred at clinically relevant exposures. Most findings were reversible or showed a tendency for reversibility and can be monitored in the clinical situation; male reproductive toxicity being an exception. Abemaciclib is teratogenic in the rat. Appropriate information concerning identified safety risks is given in the RMP, and in the SmPC.

Genotoxicity studies on metabolites M2 and M20 were not in full conformity with GLP but the missing aspects were not considered to detract the validity of the studies. It can be noted that the applicant is conducting a 2-year rat carcinogenicity study to support indications that are not advanced cancer and in addition and also preparing to conduct a 2-year mouse carcinogenicity study.

ERA: Overall, abemaciclib is expected to accumulate in the abiotic environment. While it has the potential to act as an aquatic toxicant, it does not fulfil the criteria for being classified as a PBT or vPvB candidate (environmental hazard) and the overall emission into the environment is insufficient for it to be considered an environmental risk.

Conclusion on the non-clinical aspects

The non-clinical data submitted to evaluate the pharmacology, pharmacokinetic and toxicity is considered acceptable.

Abemaciclib is not a PBT substance. Considering the submitted data, abemaciclib is not expected to pose a significant risk to the environment.

2.8. Clinical aspects

2.8.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Identifier	Objective	Abemaciclib dose	Subjects (planned), age	Dates
I3Y-MC-JPBS	Bioavailability	200 mg single dose, 0.4 mg IV dose $^{13}C_8$ abemaciclib	11 (15) healthy subjects, 18- 65	Jan 2015 – Feb 2015
I3Y-MC-JPCC	Bioequivalence and food effect	150 mg single dose	127 (128) healthy subjects, 18+	Feb 2016 – Oct 2016
I3Y-MC-JPBG	Food effect	200 mg single dose	24 (25) healthy subjects, 18- 65	Feb 2014 – Aug 2014
I3Y-MC-JPBU	Food effect	200 mg single dose	30 (36) healthy subjects, 18+	Jun2015 – Sep 2015
I3Y-MC-JPCA	QT, loperamide effect, and effect on loperamide	Single dose: 200 mg (n=20) 300 mg (n=20) 400 mg (n= 35) 600 mg (n=15)	35 (40) healthy subjects, 18-70	Feb 2016 – Jul 2016
I3Y-MC-JPBA	Safety, tolerability, activity, RP2D A: metastatic cancer B: NSCLC C: GBM D: breast cancer E: melanoma F: CRC G: + fulvestrant, HR+ breast cancer	QD: 50 mg: A 4 100 mg: A 3 150 mg: A 3 225 mg: A 3 BID: 75 mg: A 3 100 mg: A 4 150 mg: A 3 200 mg: A 7 275 mg: A 3	B: 26 C: 2 D: 25 E: 13 F: 15 B: 42 C: 15 D: 22 E: 13 G: 19	Dec 2009 – May 2015
I3Y-MC-JPBC	Safety, tolerability, in Japanese patients	BID: 100 mg (n=3) 150 mg (n=3) 200 mg (n=6)	12 (18) advanced cancer, 20+	Dec 2013 – Apr 2015
I3Y-MC-JPBV	Hepatic impairment	200 mg single dose	35 (40) healthy or hepatic impairment, 18-85	Mar 2015 – Aug 2015
I3Y-MC-JPBE	Clarithromycin effect	Single dose: 50 mg (n=26) Extension BID: 200 mg (n=20)	26 (40) advanced and/or metastatic cancer, 18+	Apr 2014 – Feb 2015
I3Y-MC-JPBF	Rifampicin effect	200 mg single dose	24 (24) healthy subjects, 18+	Oct 2014 – Nov 2014
I3Y-MC-JPBD	Mass balance	150 mg single dose, [^{14}C] abemaciclib	6 (8) healthy subjects, 18-65	Aug 2013 – Oct 2013
I3Y-MC-JPBB	Tumor response, safety, tolerability	200 mg BID	28 (20) r/r MCL patients	Apr 2013 – Sep 2015
I3Y-MC-JPBN (MONARCH-1)	Tumor response, safety, tolerability	200 mg BID	132 (128) HR+ HER2- breast cancer, 18+	Jun 2014 – Apr 2016
I3Y-MC-JPBL	Efficacy, safety,	BID:	707 (630) HR+ HER2- breast	Aug 2014 –

(MONARCH-2)	tolerability	150 mg (n=468)* placebo (n=239) + fulvestrant * n= 121 of the ITT started at 200 mg	cancer with progression on ET, 18+	Feb 2017
I3Y-MC-JPBH	Safety, tolerability, activity	200 mg BID with: letrozole (n=20) anastrozole (n=16) tamoxifen (n=16) examestane (n=15)	67 (60) HR+ HER2- breast cancer	Mar 2014 – Mar 2016
I3Y-MC-JPBM (MONARCH-3)	Efficacy, safety, tolerability	BID: 150 mg (n=327) placebo (n= 161) + anastrozole or letrozole	488 (450) HR+ HER2- breast cancer without progression on ET, 18+	Nov 2014 - Jan 2017
I3Y-MC-JPCK	Effect on metformin	400 mg single dose	40 (36) healthy subjects, 18+	Aug 2016 – Dec 2016

2.8.2. Pharmacokinetics

The single dose clinical pharmacology program has been performed in healthy volunteers, subjects with hepatic impairment, and in patients with cancer, whereas the multiple dose studies were performed in patients with advanced cancer.

Active moiety

In plasma, two major active metabolites have been identified, beside the parent compound. The metabolites M2, M18 and M20 exhibit similar potency in the enzyme binding biochemical assays as the parent drug, and have been analysed in many of the clinical trials. M18 has a lower exposure than the other species.

Absorption

An absolute bioavailability study of abemaciclib was performed in 11 healthy subject using an intravenous tracer method. The subjects received a single oral dose of abemaciclib and 6 h later on the same day an iv administration of approximately 0.4 mg $^{13}C_8$-abemaciclib. The absolute bioavailability was estimated to 45%, with modest between-subject variability (CV 19%).

Phase I and II studies have been performed with early capsule formulations (C1 and C2) and the C3 capsule formulation, and the registration studies (MONARCH 1-3) have been performed with the C3 capsule formulation (mainly the 50 mg strength). A bioequivalence study was performed to compare the tablet formulation to be marketed (50 mg, 150 mg) to the capsule formulation C3 (50 mg). Bioequivalence was shown for both Cmax and AUC for both 3x50 mg tablet and 150 mg tablet compared with the capsules used in pivotal trials, with narrow confidence intervals and ratios close to 1.

The effect of a high-fat meal on abemaciclib PK after administration of the 150 mg tablet (commercial formulation T1) was investigated in 24 healthy subjects. Food slightly increased the exposure to abemaciclib, with a 13% higher AUCinf and 29% higher Cmax in the fed state. A minor increase in the exposure to the

metabolites M2 and M20 was also observed (AUCinf 11% and 2% higher, respectively). No difference in tmax was detected.

Distribution

The geometric mean systemic volume of distribution is approximately 750 L (69% CV).

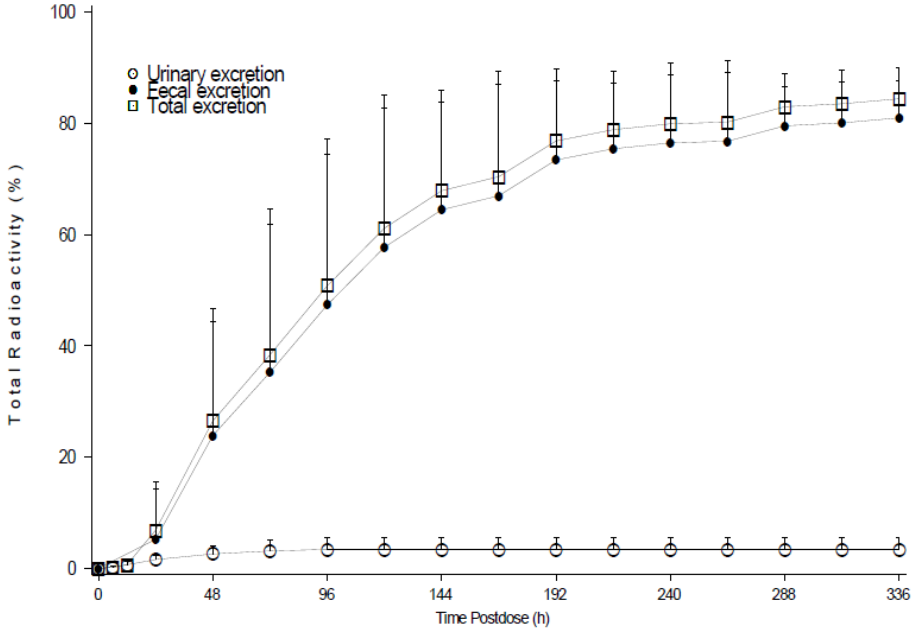
In vitro protein binding of abemaciclib (0.3-10 µM) in human plasma as well as human liver microsomes was tested using a 6 h equilibrium dialysis and at 0.3 µM (average clinical Cmax) 97% of the drug was bound to plasma proteins. In a new in vitro study including also the active metabolites, the average protein binding at 1 µM was 94% for abemaciclib, 92% for M2 and 98% for M20. These data were used in the calculation of active moiety.

Ex vivo plasma protein binding of abemaciclib and its metabolites was also determined in plasma samples from the hepatic impairment study, taken approximately 6 hours after dose. Equilibrium dialysis was used. In healthy subject, protein binding of abemaciclib was 96%, M2 93% and M20 98%. Protein binding was lower in subjects with severe hepatic impairment.

Elimination

A mass-balance study was performed, where 6 healthy subjects received a single oral dose of 150 mg LY2835219 containing [14C]-LY2835219 (approximately 5 µCi) administered as an oral solution under fasting condition (10 h before and 4 hours after dose). The overall recovery in the study was 84.4%. A mean (±SD) of 81.0 (±6.71)% of the dose was excreted in faeces and 3.43 (±2.20)% was excreted in urine through the last collection interval (336 hours postdose). Most of the administered radioactivity was recovered in the first 192 hours postdose in faeces (73.4%). Due to the low amounts of drug retrieved in urine, metabolite profiling was only performed in faeces. Parent drug and 6 metabolites (M1, M2, M18, M20, M21, and M22) were identified in faeces, and together they added up to 59% of the administered dose, representing approximately 70% of recovered radioactivity. The major metabolite excreted was the oxidative metabolite M2

Figure 2. Arithmetic mean (+SD) cumulative excretion of total radioactivity in urine and faeces, overall, after oral administration of a single 150-mg dose of [14C]-LY2835219 in Healthy Subjects

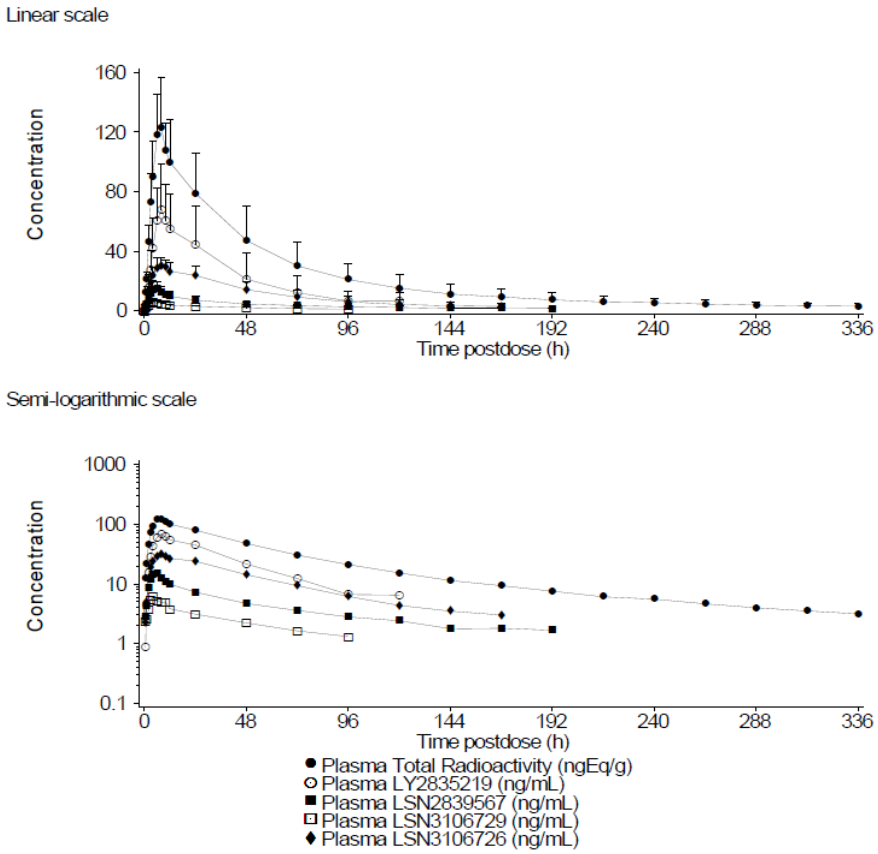


P-gp as well as BCRP substrate assessment of abemaciclib and M2 was conducted using Madin-Darby canine kidney (MDCK) cell monolayers transfected with human multi-drug resistance gene (MDR1) at a substrate concentration of 5 µM. Both entities were shown to be substrates for both P-gp and BCRP. In an in vitro study in HEK cells transfected with transporter genes, it was concluded that abemaciclib was not a substrate of OATP1B1 but technical issues precluded conclusions on OATP1B3.

In vitro studies using human recombinant CYPs and substrate depletion indicate that the CYP-catalysed metabolism of both abemaciclib and its active metabolites M2 and M20 is almost entirely catalysed by CYP3A4.

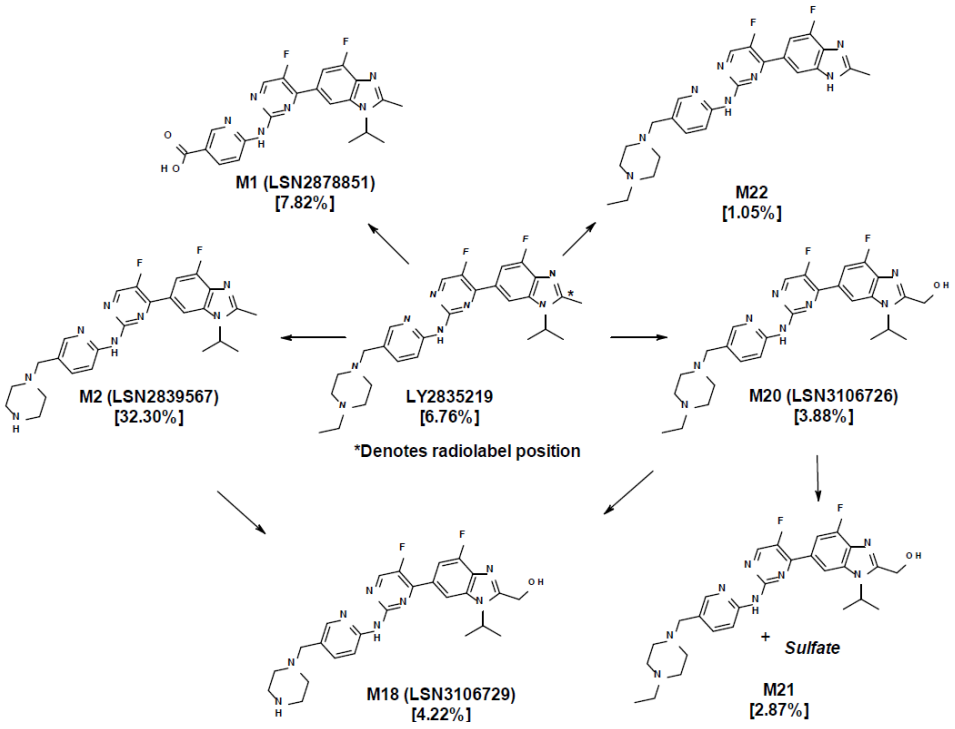
The plasma profile of total radioactivity, parent compound and major metabolites after a single dose of abemaciclib are displayed in Figure 2. Parent compound constituted 34% of total plasma radioactivity whereas the major metabolites M2 and M20 were 13 and 26%, respectively. M18 was approximately 5% of total radioactivity.

Figure 3. Arithmetic mean (+SD) concentrations of abemaciclib (LY2835219), metabolites, and total radioactivity in plasma after oral administration of a single 150-mg dose [14C]LY2835219 in Healthy Subjects. (LSN3106726=M20, LSN2839567=M2, LSN3106729=M18).



The metabolism scheme proposed by the Applicant is shown below:

Figure 4. Abemaciclib (LY2835219) and metabolites eliminated in faeces [as % dose] following a single oral 150-mg dose of abemaciclib containing approximately 5 µCi of [14C]-abemaciclib in healthy human subjects.



An interaction study with clarithromycin confirmed the role of CYP3A4 in abemaciclib metabolism. The estimated fraction metabolised by CYP3A4 (fm) in the PBPK analysis was 0.89. Metabolites M2 and M20 are both substrates for CYP3A4, and CYP3A4 metabolism seems to be important for their elimination. M2 is also retrieved in faeces. M2 is a substrate for P-gp as well as BCRP, and these transport proteins may contribute to the active secretion of M2.

Dose proportionality and time dependencies

Single-dose data did not indicate any major deviation from dose proportionality. In the multiple dose, dose-escalation trial, preliminary analysis of PK data from the initial 4 dose levels tested with once daily dosing (50, 100, 150, and 225 mg Q24H) indicated less than dose-proportional increases in exposure. Due to this tendency, a twice-daily schedule was introduced, and doses from 75 to 275 mg BID were tested, with no major deviation from dose proportionality observed. In the QT study doses between 200 and 600 mg were tested, without signs of non-linearity. In both the popPK-modelling and in the PBPK model, a non-linear component is however included, suggesting lower bioavailability at higher doses.

In study JPBA, the accumulation index at the clinical doses 150 and 200 mg was estimated to 2.5-2.6, which is in line with what would be expected for a drug with a half-life around 24 hours.

Population pharmacokinetics

A population approach was used to characterize the PK of abemaciclib in target population and healthy subjects, characterize the between-patient variability, assess intrinsic and extrinsic factors that could significantly influence abemaciclib, and estimate individual patient exposure for exposure-response analyses.

The analyses are based on the SAEM estimation method and the final models have not met the criteria for convergence and hence statistical testing based on the based on the objective function value is not valid. Due to the computational intensity of the mechanistic model no formal covariate search was conducted instead a graphical analysis was used to determine inclusion of covariates. The Applicant states that the graphical covariate evaluation based on Bayesian posthoc estimates (eta values) is valid due to low shrinkage. However, it is difficult to assess whether the parameter estimates are affected by the non-convergence (the Monte Carlo noise) as it seems to have been present throughout the model development process. The issue of Monte Carlo noise introduces an uncertainty in the reliability of the population PK parameter estimates. The results from the population PK analysis are not accepted due to the uncertainties in the model development, although the population PK results are not pivotal for this application and further model development is not pursued. However, for future use of the population PK model issues regarding non-convergence, handling of BLQ data, and coding of time varying covariates (e.g. diarrhoea) need to be addressed.

Special populations

	Age 65-74 (n, %)	**Age 75-84 (n, %)**	**Age 85+ (n, %)**
Controlled trials (N = 1152)	331(28.7)	121 (10.5)	12 (1.0)
MONARCH 2 (N=664)	173(26.1)	66(9.9)	5(0.8)
MONARCH 3 (N=488)	158(32.4)	55(11.3)	7(1.4)
Non-controlled trial: MONARCH 1 (N=132)	32 (24.2)	9(6.8)	1(0.8)

As the population PK analysis provided is not of acceptable quality, the evaluation of co-variates performed with the model cannot be used to draw conclusions on the influence of renal function, age, gender or weight on abemaciclib pharmacokinetics.

No dedicated renal impairment study was performed. Patients with mild and moderate renal impairment were included in the pivotal studies.

A single 200 mg dose pharmacokinetic study of abemaciclib in subjects with varying degree of hepatic impairment, was performed. Subjects with mild and moderate hepatic impairment had a similar average abemaciclib drug exposure as subjects with normal liver function, but with a tendency to lower Cmax. Subjects with severe hepatic impairment had geometric least square (LS) mean AUC0-∞ of abemaciclib that was 2.09 (90% CI: 1.33, 3.28) times higher than that observed in control subjects. The average abemaciclib half-life was longer in patients with severe hepatic impairment. A slower absorption was observed in subjects with hepatic impairment, and tmax was increased from 7h in subjects with normal liver function to 24 h in subjects with severe hepatic impairment. On the other hand, a lower exposure of the active metabolites M2 and M20 was observed with increasing grade of hepatic impairment.

When total analytes were considered (abemaciclib + M2+M20) there was only a marginal difference between the groups, the increase in parent drug exposure was outweighed by decreased metabolite exposure (ratio of geometric means for AUCinf was 0.82, 0.82 and 1.20 for mild, moderate and severe HI, respectively, compared with normal liver function). The protein binding of abemaciclib as well as of the metabolites decreased with increased degrees of hepatic impairment. The average fu of abemaciclib was increased from 3.7% in subjects with normal hepatic function to around 5% in mild and moderate hepatic impairment and 7.8% in plasma from subjects with severe hepatic impairment. For active moiety (defined as the sum of unbound potency adjusted exposure to parent+M2+M20) , the geometric LS mean AUC(0-∞)u was similar to that observed in control subjects in subjects with mild or moderate hepatic impairment but were 2.35 time s higher, respectively, in subjects with severe hepatic impairment compared to control subjects.

A separate phase I study was performed in Japanese subjects. Tolerability of the 200 mg BID dose was confirmed in this population. The PK variability was large, but the average exposure (AUC0-T,ss) in the 200 mg group (3020 ngxh/ml; CV 73%) was found to be similar to the exposure after 200 mg abemaciclib in the previous phase I study (JPBA; 3000 ngxh/ml; CV 69%). No further data on the influence of race on abemaciclib pharmacokinetics is available.

In the popPK model, the Applicant has included diarrhoea as a covariate on bioavailability. The effect of diarrhoea on abemaciclib pharmacokinetics has not been further discussed in the application.

Pharmacokinetic interaction studies

In vitro data

A full in vitro DDI program has been performed. The cutoff for clinical relevance of systemic interactions (50xCmax,u) was 0.5 µM. Using the absorption parameters proposed by the Applicant, the hepatic inlet cutoff (25xCmaxu, inlet) was 1.9 µM. Worstcase concentration in the gut 0.1xdose/250 ml) would be 160 µM.

No direct inhibition by abemaciclib or the metabolites M2 or M20 of any of the CYP enzymes tested was observed at plasma concentrations relevant for systemic exposure. A slight inhibition (28% and 33%, respectively) of CYP3A4 and CYP2C19 was observed at the highest concentration tested (12.5 uM). No data was available at concentrations relevant for gastrointestinal exposure. The risk for time-dependent inhibition could be excluded at systemic concentrations, but the concentration range did not cover concentrations relevant for gastrointestinal exposure.In vitro induction was studied in two studies with human hepatocytes. No induction was observed, but a trend to a dose-dependent decrease in mRNA expression was seen for some of the enzymes. No data was available at concentrations relevant for gastrointestinal exposure. A clinical DDI study is underway to address potential effects of abemaciclib on CYP enzymes (see below).

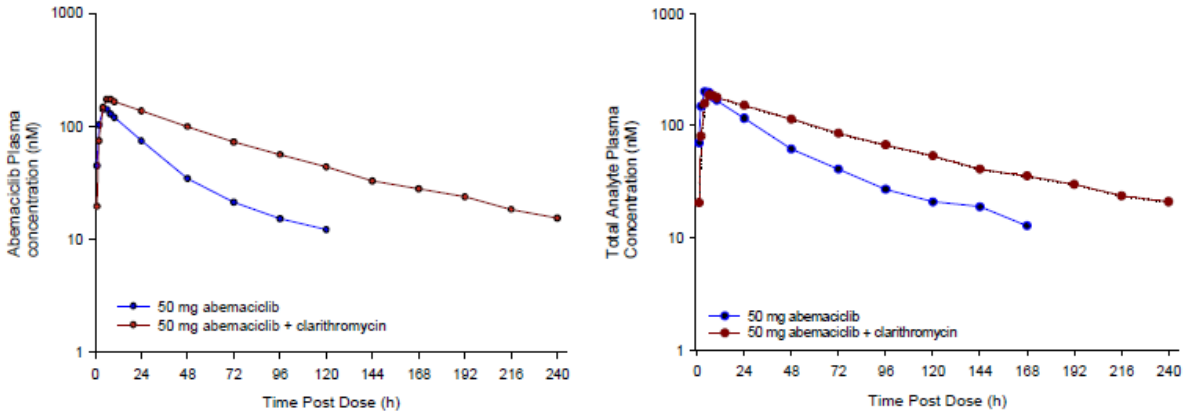
Abemaciclib inhibited both P-gp and BCRP in vitro in membrane vesicles. Systemic P-gp inhibition is not likely based on the in vitro data, but a risk for inhibition of both P-gp and BCRP in the gastrointestinal tract, as well as systemic BCRP, could not be excluded. A DDI study with the P-gp substrate loperamide was performed (see below), but no study with a BCRP substrate was performed. Inhibition of OAT transporters were not seen, and OATP1B1 and OATP1B3 were inhibited only at concentrations higher than the cut-off for clinical relevance. A risk for clinical inhibition of OCT1, OCT2, MATE1 and MATE2 could not be excluded based on in vitro data. A clinical DDI study with metformin was performed (see below).

In vivo data

In vivo DDI studies with clarithromycin and rifampicin (abemaciclib as a victim) as well as metformin and loperamide (abemaciclib as a perpetrator) were performed and are summarised below. The applicant is recommended to submit data generated from an ongoing DDI study to address abemaciclib as a perpetrator for CYP-medicated drug-drug interactions.

A 2-period fixed sequence study was performed to investigate the impact of CYP3A inhibition by clarithromycin on abemaciclib metabolism. In period 1, a single oral 50 mg abemaciclib dose was administered, followed by 7 days washout. In period 2, clarithromycin 500 mg was administered twice daily for 5 days. On day 5, abemaciclib was administered as a single, 50-mg dose approximately 30 minutes following the clarithromycin dose. Clarithromycin dosing was continued for 7 more days following single-dose administration of abemaciclib. PK sampling for abemaciclib as well as M2, M18, and M20 was performed 7 days after dose in period 1 and 10 days after dose in period 2. Clarithromycin co-administration increased drug exposure after a single dose abemaciclib. The effect was larger on abemaciclib (AUCinf increased 3.4 fold) than on active moiety (defined as the potency adjusted sum of unbound parent+M2+M20) which increased 2.5-fold.

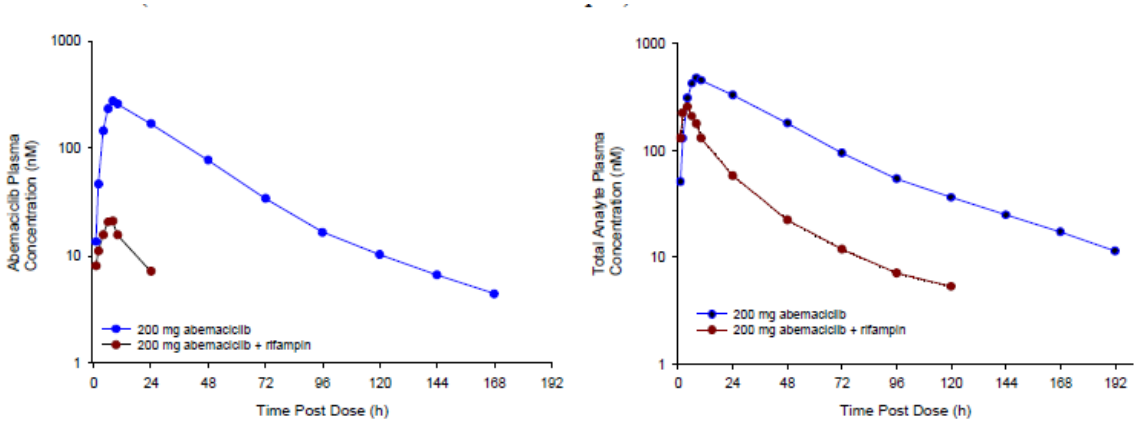
Figure 5. Arithmetic mean plasma concentration-time profiles of abemaciclib (left panel) and total analytes (right panel) following a single dose of 50 mg abemaciclib alone or with 500 mg clarithromycin Q12H.



A two-period, fixed-sequence study was performed to investigate the impact of CYP3A induction by rifampin on the metabolism of abemaciclib in healthy subjects. Abemaciclib was administered orally as a single, 200-mg dose on 2 occasions; alone on Day 1 of Period 1 and in combination with 600 mg rifampin on Day 7 of Period 2, after 6 days of once daily rifampicin dosing.

Rifampicin co-treatment decreased abemaciclib exposure substantially, AUCinf decreased by 95%. Also the metabolites M2 and M20 had decreased exposure, but the effect was smaller (65% and 80%, respectively).

Figure 6. Arithmetic mean plasma concentration-time profiles of abemaciclib (left panel) and total analytes (right panel) following a single dose of 200 mg abemaciclib alone or with 600 mg once-daily rifampin in healthy subjects.

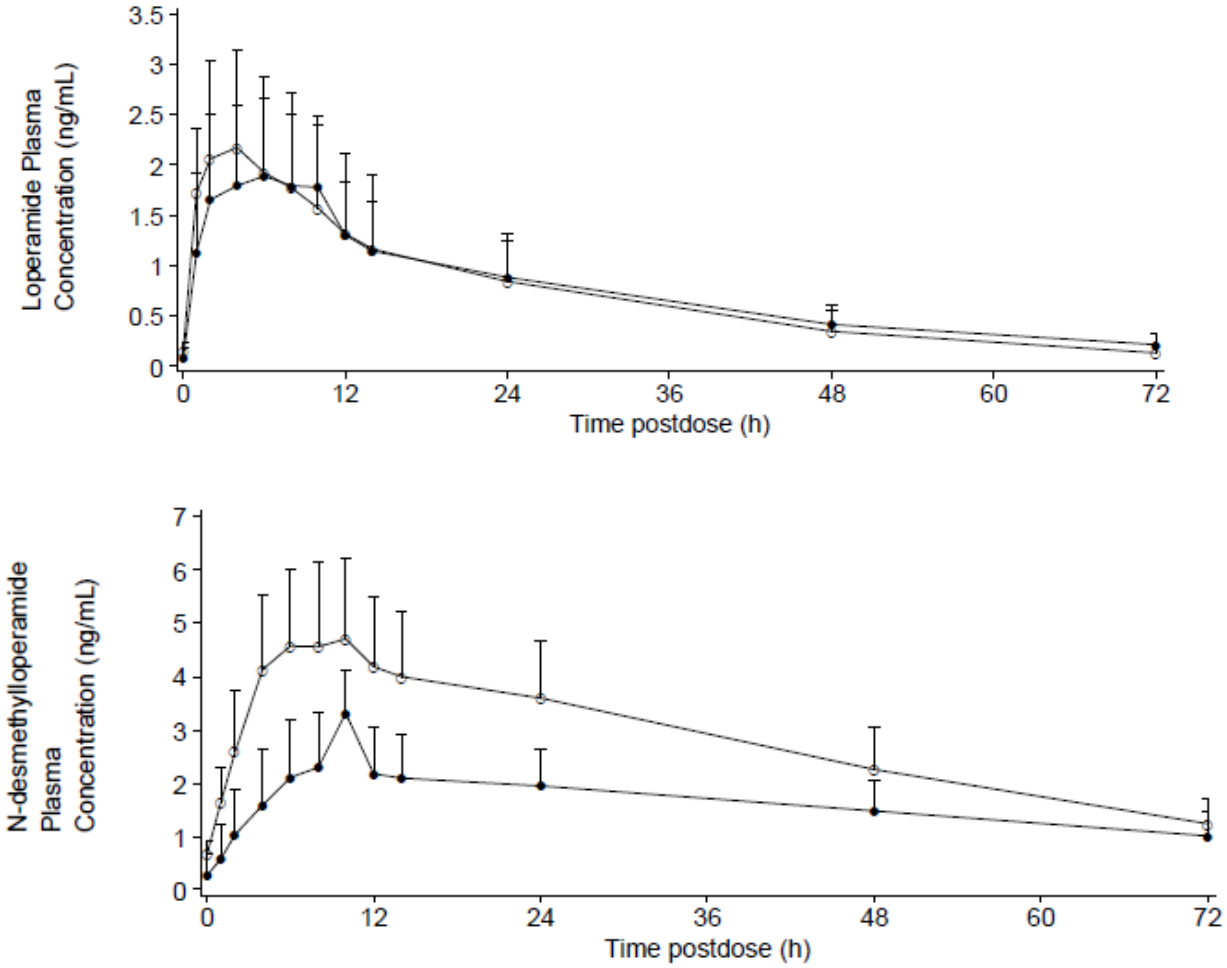


A 4-period, randomized, placebo controlled, crossover study was performed in healthy subjects to investigate the effect of 400 mg abemaciclib on renal transporters OCT2, MATE1, and MATE2-K, as assessed by the PK of metformin, and on glomerular filtration rate (GFR) as assessed by intravenous (IV) iohexol clearance (CL)**.** Forty subjects (4 male, 36 female) were randomized to 1 of 4 treatment sequences, and received abemaciclib or placebo during 4 periods (2 metformin assessment periods and 2 iohexol assessment periods). During the metformin assessment periods, subjects received a single oral 400-mg dose of abemaciclib or placebo, followed by a single oral 1000-mg dose of metformin 5 hours later. During the iohexol assessment periods, subjects received a single oral 400-mg dose of abemaciclib or placebo followed by 5 mL (3235 mg) of Omnipaque 300 (iohexol) solution 8 hours later, infused over approximately 15 minutes. Metformin was assessed both in plasma and in urine for 36 hour post metformin dose.

Abemaciclib significantly increased metformin exposure compared to placebo, with increases in AUC0-∞ and Cmax by 37% and 22%, respectively, and significantly decreased metformin CL, with decreases in renal clearance (CLR) and renal secretion clearance (CLRS) of 45% (CLR ratio 0.550) and 62% (CLRS ratio 0.381), respectively. A single oral dose of 400 mg abemaciclib, compared to placebo, had no effect on GFR as measured by iohexol clearance

A DDI study with the P-gp substrate loperamide was also performed. Following a single dose of 8 mg loperamide coadministered with 400 mg abemaciclib, the mean AUC(0-tlast), AUC(0-∞), and Cmax values for loperamide were increased by 13%, 9%, and 35%, respectively, compared to 8 mg loperamide administered alone or with placebo. Larger increases were observed for N-desmethyl loperamide, the principal metabolite of loperamide, increased 94% in AUC0-tlast 47% in AUC0-∞ and 133% in Cmax, when loperamide was coadministered with abemaciclib.

Figure 7. Arithmetic mean (+SD) plasma loperamide (upper graph) and N-desmethylloperamide (lower graph) concentration versus time profiles following single oral doses of 8 mg loperamide alone/8 mg loperamide + placebo (black symbols) and 8 mg loperamide + 400 mg abemaciclib (open symbols) in healthy subjects.



An ongoing DDI study using a cocktail approach is performed to assess the effect of multiple doses of abemaciclib on the PK of the CYP substrates midazolam, caffeine, warfarin and dextromethorphan. An interim analysis presented does not indicate clinically relevant effects on the investigated substrates, but assessment of the study awaits final data that the Applicant is recommended to submit.

Pharmacokinetic data from a Phase 1b, multicentre, outpatient, nonrandomized, open-label study to examine the safety and tolerability of abemaciclib in combination with letrozole, anastrozole, tamoxifen, or exemestane in patients with HR+ and HER2- mBC was also provided. No single-agent data was provided, and dose-adjustment was allowed during the study, and thus no formal evaluation of a potential pharmacokinetic interaction could be performed. Comparing data from day 1 and day 28, as well as comparing with historical data did not indicate any major PK interaction between abemaciclib and the endocrine acting agents.

Abemaciclib is a weakly basic drug that shows pH dependent solubility, with lower solubility at pH 6.8 than at lower pH. No clinical study to evaluate the impact of acid-reducing agents on abemaciclib absorption has been performed. The Applicant argues that as the highest dose of abemaciclib (200 mg) is soluble in less than 250 mL

up to pH 6.8, coadministered acid-reducing agents are unlikely to have an effect on the absorption and exposure of abemaciclib. In addition, the solubility of abemaciclib drug substance in simulated fasted and fed intestinal fluid is much greater than at pH 6.8, at 5.3mg/mL and 31 mg/mL, respectively.

No DDI study with oral contraceptives has been performed.

Pharmacokinetics using human biomaterials

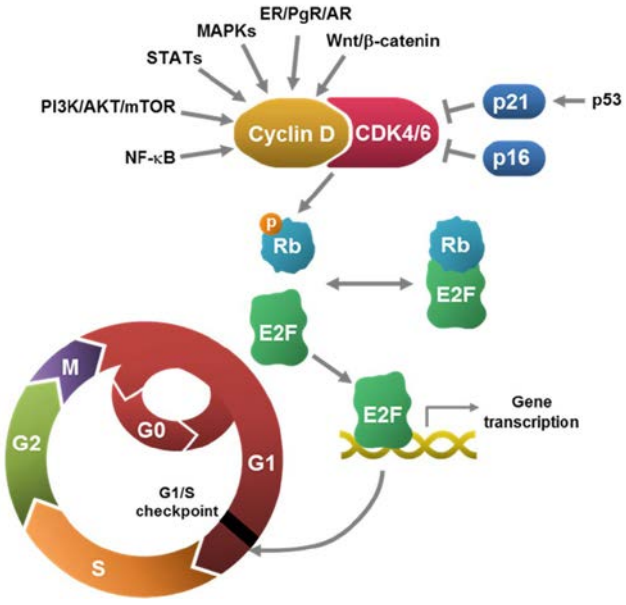
2.8.3. Pharmacodynamics

Mechanism of action

Mechanism of action

Abemaciclib is an inhibitor of CDK4 and CDK6 and was most active against Cyclin D1/CDK4 in enzymatic assays. In breast cancer, Cyclin D1/CDK4 has been shown to promote phosphorylation of the retinoblastoma protein (Rb), cell proliferation, and tumor growth. Abemaciclib inhibits Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth in preclinical models following short duration target inhibition. In ER+ breast cancer cell lines, sustained target inhibition by abemaciclib prevented rebound of Rb phosphorylation and cell cycle reentry, resulting in senescence and apoptosis. In vivo, abemaciclib as a single agent dosed daily without interruption at clinically relevant concentrations in breast cancer xenograft models resulted in reduction of tumor size.

In addition to inhibiting phosphorylation of Rb, inhibition of CDK4 and CDK6 resulted in inhibition of topoisomerase II alpha (topoIIα) expression.



Genetic differences in PD response

Clinically, a molecular correlate of variable sensitivity to CDK 4/6 inhibition has not been identified; in registration trials for the approved inhibitors plabociclib and ribociclib no compelling evidence of differential efficacy in subgroups defined by Cyclin D1, RB or P16 mRNA or protein expression has emerged.

Preclinical findings indicate that there may be a molecularly well-defined group of patients with compromised benefit. Different levels of the CDK-RB-E2F axis may be important to further characterize in treated patients, preferably in the randomized treatment setting, including the CDK4/6 target and other cyclin-dependent kinases, RB and related transcriptional repressors p107 and p130, and redundancy of E2F and downstream transcriptional effects.

MONARCH-2 and MONARCH-3

According to the MONARCH-2 and MONARCH-3 study reports, tumor tissue (FFPE) was required to be provided by investigator sites in conjunction with enrollment; the use of IHC, FISH, RNA and gene-expression profiling is mentioned as methods to investigate CDK4 and CDK6 pathway components (for example, Rb) and markers relevant to breast cancer pathogenesis. Correlating findings with clinical efficacy data was foreseen. Blood and plasma samples were also to be collected for similar purposes.

No findings regarding these exploratory biomarker analyses have been made available. The applicant expects to have clinical trial biomarker data for MONARCH 3 in the fourth quarter of 2018. The experimental work is ongoing and should yield instructive data by the first quarter of 2019. A category 3 post-authorization measure is proposed encompassing biomarker analyses in MONARCH 2 and MONARCH 3.

Primary and Secondary pharmacology

Relationship between plasma concentration and efficacy

PK/PD analyses were provided for objective response rate and progression free survival (MONARCH 1) and in MONARCH 2 a dynamic population PK/PD model was developed to describe the relationship between dose, plasma concentration (total active moiety), tumour size and progression free survival.

Relationship between plasma concentration and safety

Dose was identified as a significant factor related to diarrhea occurrence and timing of onset.

In the MONARCH 2 and MONARCH 3 populations, there was a relationship between dose/exposure and neutropenia.

Concentration QT

Abemaciclib does not cause clinically significant Fridericia's corrected QT (QTcF) prolongation. In an exposure-response analysis in healthy subjects at exposures comparable to those achieved for a 200-mg twice-daily dose, the upper bounds of the 2-sided 90% confidence interval (CI) for the effects of abemaciclib and its active metabolites in placebo- and baseline-corrected QTcF were less than 10 msec.

2.8.4. Discussion on clinical pharmacology

A fundamental question that determines the usefulness of PK data of abemaciclib, is to find a reliable definition of active moiety. In most studies, both parent compound and the active metabolites M2 and M20 were measured, sometimes also M18. A sum of parent+M2 +M20 was first proposed as the active moiety, but in the second round of assessment the Applicant proposed a new definition of active moiety, namely sum of potency adjusted unbound parent+M2+M20. It is agreed that the new active moiety appears more scientifically sound, but the issue remains that the active moiety concept is very hypothetical and highly dependent on the input values of e.g. potency and protein binding. Based on the inherent uncertainties in the use of an active-moiety estimation, the DDI results and PBPK output should not be over-interpreted. The dose adjustments for drug interactions and organ impairment need to be modest to avoid risk for underexposure, and followed by intensive monitoring of toxicity.

A slight increase (13%) in abemaciclib exposure after administration of a 150 mg tablet together with a high-fat meal was observed. The influence of food was very small compared to overall variability, and it is agreed that this food-effect is unlikely to be clinically relevant. The recommendation that abemaciclib can be administered with or without food is agreed.

The mean recovery in the mass-balance study was 84%, and of the recovered dose, around 70% was identified. This is somewhat lower than recommended in guideline. However, it seems unlikely that the study would have missed any major elimination pathway or major metabolite. Only a small fraction of the dose (3%) was found in urine, indicating a minor role of renal elimination. In vitro and in vivo data confirm that CYP3A4 is the most important enzyme in the metabolism of abemaciclib. The two major plasma metabolites, M2 and M20, are excreted in faeces or further metabolised, mainly by CYP3A4.

Only 7% was retrieved as parent compound in faeces, which suggests high absorption. A low amount of unchanged drug in faeces is in itself however not enough to conclude high permeability. There are no data presented regarding abemaciclib stability in the gastrointestinal tract. No in vitro permeability data was presented.

Abemaciclib as well as M2 were shown to be in vitro substrates of P-gp and BCRP, but mass balance data suggest that P-gp or BCRP transport is unlikely to be of importance for absorption and elimination of parent compound. Excretion of the active metabolite M2 into faeces may however be mediated by P-gp/BCRP efflux, which suggests a risk for increased M2 levels if co-administering P-gp inhibitors. A clinical DDI study with the CYP3A4 as well as P-gp inhibitor clarithromycin has been performed, but the relative role of P-gp- and CYP3A4 inhibition in the increase in M2 exposure cannot be elucidated based on these data.

The in vitro studies submitted do not indicate that abemaciclib or its metabolites are substrates of the hepatic transporters OATP1B1/ 3 or OCT1. There are however technical issues with some of the experiments. The applicant is recommended to submit additional in vitro data on OATP1B3 to facilitate the final conclusion regarding the role of active hepatic uptake

Data suggests an approximately dose-linear pharmacokinetics of abemaciclib, and the observed accumulation is roughly in line with the reported half-life of abemaciclib, indicating no major time dependency. Data on metabolite exposure is however not sufficiently presented to address a potential time dependency in metabolism pattern, but as the issue of time dependency is unlikely to largely affect overall conclusions, this issue is not pursued.

According to the CSR of study JPBA, the reason for choosing the twice-daily dosing was a concern that the absorption of abemaciclib would decrease at higher doses with the once daily dosing. With more data emerging

this saturation tendency was no longer observed, and the scientific rationale for a BID dosing appears somewhat unclear. Given that all pivotal trials are performed with this dosing frequency, this issue is not further pursued.

Special populations

Given that the population PK modelling is considered inadequate, the evaluation of renal function, age, gender, race and weight performed with the population PK model cannot be used. As no other analysis is available for many of these factors, data is lacking for many special populations. It is acknowledged that influence of these factors are difficult to study without a popPK model, as the active metabolites also need to be taken into account to address clinical relevance of any effects observed. As it is considered unlikely that any of these co-variates alone would have a major impact on the PK of abemaciclib, and that the variability in PK in general is handled with dose adjustments, this issue is not further pursued and lack of data is accepted. To compensate for uncertainty in the covariate effects of body weight, the relationship between progression free survival and body weight was investigated, as further described in the discussion of exposure-response relationships.

Neither abemaciclib nor its active metabolites are excreted unchanged in urine, and no effect of mild or moderate renal impairment is expected. In general, an effect of severe renal impairment on hepatically eliminated drugs cannot be excluded and the Applicant has not discussed the lack of data in severe renal impairment further. As a potential increased exposure to abemaciclib can be handled with dose adjustments based on tolerability, the lack of data in severe renal impairment is however considered acceptable.

The Applicant has performed a full hepatic impairment study, and the overall design appears relevant. In general, the effect of hepatic impairment on the pharmacokinetics of abemaciclib and its metabolites was modest. Total abemaciclib exposure increased with increased severity of hepatic impairment, whereas the exposure to the active metabolites decreased, leading to a similar exposure to active moiety for subjects in all groups. A decreased protein binding in subjects with severe hepatic impairment however lead to substantially higher unbound active moiety exposure in patients with severe HI (2-3 times).The Applicant proposes that no dose adjustment is needed in patients with mild and moderate HI, which is endorsed. In patients with severe hepatic impairment, a decrease in dosing frequency to once daily is recommended based on the longer half-life and the 2-3 times higher exposure to unbound active moiety observed in patients with severe hepatic impairment. This recommendation is agreed.

It seems likely that diarrhoea can affect abemaciclib absorption, and diarrhoea was identified as a covariate in the popPK. The effect of diarrhoea on abemaciclib PK is not possible to quantify based on the popPK model submitted. This issue is not further pursued as diarrhoea is very common in the study and will be treated pharmacologically in the clinical situation.

Interactions

Abemaciclib is a CYP3A4 substrate and is therefore significantly affected both by CYP3A4 inhibitors and inducers.

- Effect of abemaciclib on other medicines (as perpetrator)

The in vitro data on CYP inhibition and induction were not fully conclusive, but this is not an issue as the Applicant is performing a cocktail DDI study to address potential effects of abemaciclib on different probe CYP substrate. An interim analysis did not indicate any clinically relevant CYP inhibition or induction. The applicant is recommended to submit the final results as soon as available.

Abemaciclib inhibited BCRP and P-gp in vitro. A clinical study with loperamide as a P-gp substrate has been performed. No DDI study has been performed to address the risk for clinical interaction with BCRP substrates. Although unfortunate, this is acceptable due to the low number of known sensitive substrates. The interpretation

of the DDI study with loperamide is not straight-forward. Only a marginal increase in loperamide Cmax and AUC was observed, suggesting a transient effect of abemaciclib mainly during loperamide absorption, possibly through mild P-gp inhibition. The effect on the metabolite was substantial (almost doubled AUC up to 72 hours).The mechanistic explanation for this is unknown, but P-gp inhibition may contribute. The Applicant discusses the potential clinical relevance for co-administration with loperamide, and it is agreed that as the metabolite is claimed to be substantially less potent than the parent compound, loperamide can be used without dose adjustments together with abemaciclib.

In vitro inhibition of OCT1, OCT2, MATE1 and MATE2, but not of OATP1B1 and 1B3, was observed at clinically relevant concentrations if the sum of the inhibitory effects of abemaciclib and its metabolites are taken into account. To address the relevance of the inhibitory effects on OCT2, MATE1 and MATE2, and given that an increase in creatinine was observed in the clinical studies, a DDI study with metformin was performed. The design of the metformin DDI study allowed a discrimination between effects on renal filtration and active transport, and a 37% increase of metformin exposure was shown to occur without affecting GFR, thus being attributed to inhibition of renal secretion. This is in line with abemaciclib being an in vitro inhibitor of OCT2, MATE1 and MATE2. These data support the theory put forward by the Applicant that the creatinine elevations observed clinically is caused by inhibition of renal transport proteins.

- Effect on abemaciclib (as victim)

The interaction study with clarithromycin verifies a role of CYP3A4 in abemaciclib metabolism. The study is also the basis for a starting dose reduction if CYP3A4 inhibitors are used together with abemaciclib. The interpretation of the study is complicated by several factors. The different effect on different metabolites and the inherent uncertainties in the relative contribution of these entities to efficacy and safety makes quantitative use of the data in dose adjustments difficult. In addition, the study design is not optimal, it is performed at a dose level of abemaciclib substantially lower than clinical dose and 4 days of clarithromycin pre-treatment is probably somewhat short to obtain full effect on CYP3A4. The mechanistic interpretation is also complicated by the fact that both major metabolites are substrates of CYP3A4, and M2 is also excreted into faeces via P-gp (which is also inhibited by clarithromycin).

The general recommendation to avoid strong CYP3A4 inhibitors is agreed given the limitations of the DDI study with clarithromycin, the unclear relevance of active moiety and the knowledge that stronger inhibitors than clarithromycin may give even larger effects on abemaciclib exposure than clarithromycin. When strong CYP3A4 inhibitors anyhow need to be used the dose should be reduced to 100 mgx2, and patients should be further monitored for toxicity. To avoid a risk for under-exposure, no initial dose adjustments are proposed for patients taking moderate or weak inhibitors, but regular toxicity monitoring followed by the possibility to reduce the dose is deemed sufficient for these patients.

The Applicant has built a complex PBPK model describing the effects of CYP3A4 interactions on the exposure to abemaciclib and its active metabolites, and this effort is acknowledged. There are however several issues with this model, and in addition, there are uncertainties about the relative contribution of the active metabolites to efficacy and safety that preclude the use of modelling quantitatively in developing dosing recommendations. Data from the rifampicin study shows a large effect of the strong inducer rifampicin on the exposure of abemaciclib as well as its active metabolites. It is agreed with the Applicant that this large decrease in drug exposure cannot be handled with dose adjustments, and that CYP3A4 inducers should be avoided.

The phase I study evaluating the combination between abemaciclib and letrozole, anastrozole, tamoxifen, or exemestane was not designed to evaluate a potential drug-drug interaction between the agents. The two drugs were given together during the whole study period, and no single-agent data are available from the study. In

addition, dose adjustments were performed before the steady state data were collected. The data can thus not be used to draw quantitative conclusions on the interaction potential. It is however agreed with the Applicant that the data do not suggest any large PK interaction between abemaciclib and any of the endocrine therapies.

It is agreed that the risk for an interaction with acid reducing agents appears low as the maximum dose of abemaciclib can be dissolved in 250 mL at all pH relevant for the stomach. No DDI study is needed.

Exposure-response relationship

The Applicant has provided exposure-response analyses for relevant endpoints. However, it is important to point out that the uncertainty in the validity of the predicted exposures is propagated onto the results of the exposure-response analyses.

Further, dose reductions limit the interpretability of exposure-response analyses. Although dynamic exposure has been used for PFS and neutrophil relationships, the simulated dose-response curves assumes a static dose and the comparison to the observed average dose does not fully incorporate the duration of each dose level.

The Kaplan-Meier quartile analyses for PFS and the effects of body weight display no clear relationship between body weight and PFS.

The effort to provide exposure-response relationships for efficacy and safety are acknowledged, however, the uncertainty of the validity of model predicted PK, and confounding factor of dose reductions in interpreting exposure-response and subsequent simulated dose-response relationships limits the value of exposure-response in support for dose selection. The exposure-response relationships are not further pursued as it is not perceived that higher doses would be tolerable and the proposed initial doses are reduced based on adverse events.

2.8.5. Conclusions on clinical pharmacology

There is no objection to an approval of Verzenios from a clinical pharmacology point of view.

A preclinical-clinical discordance in the impact of RB function on sensitivity to CDK4/6 inhibition may indicate a group of patients with compromised benefit. The applicant is recommended to submit biomarker analyses for MONARCH 2 and 3.

2.9. Clinical efficacy

2.9.1. Dose response study(ies)

I3Y-MC-JPBA

Objectives

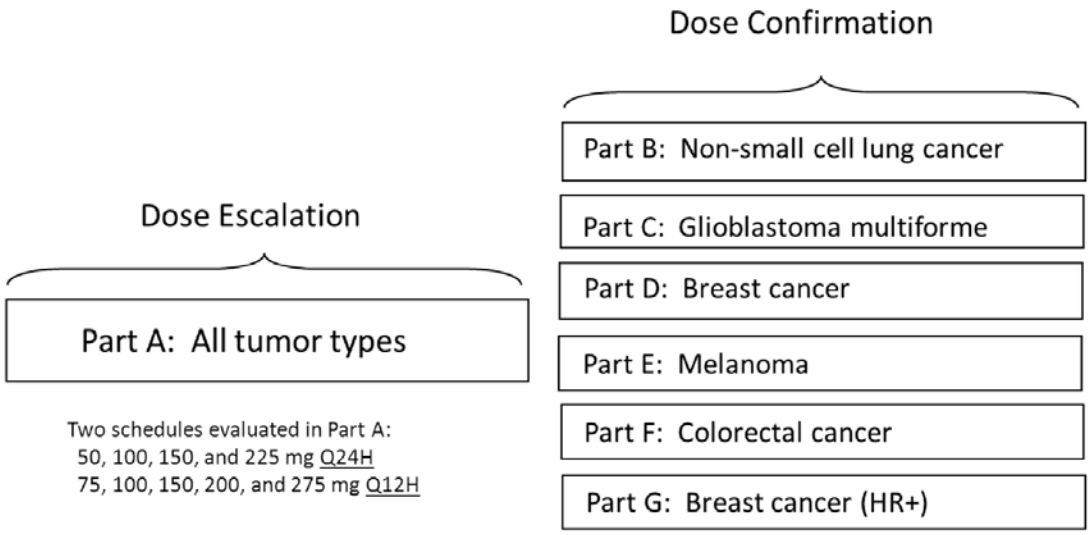
The primary objective of this study was to evaluate the safety and tolerability of LY2835219 when administered orally to patients with advanced cancer.

The secondary objectives of this study were to:

- determine the PK of LY2835219

- evaluate pharmacodynamic and predictive biomarkers
- document the antitumor activity of LY2835219
- establish a recommended dose range for Phase 2 studies.

Study design

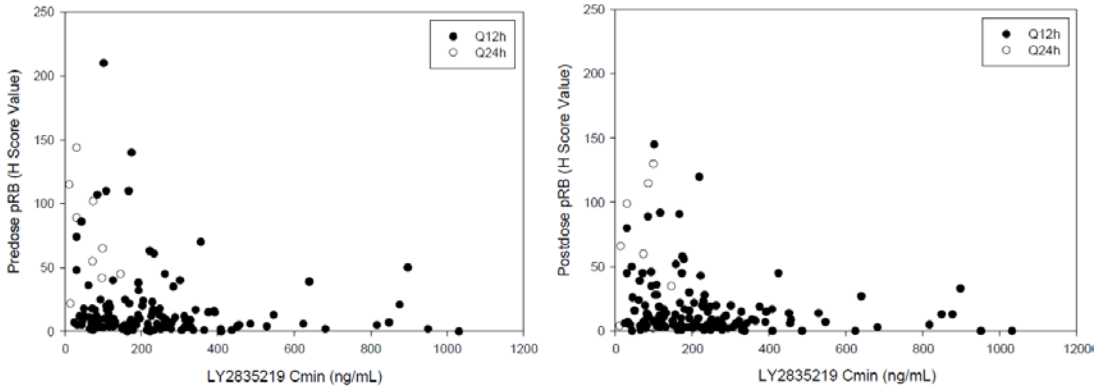


Results

The numbers of patients exposed to different doses in the respective parts of the study are tabulated in section 3.3.

- The applicant references a murine xenograft model (Tate et. al. Clin Cancer Res 2014) as support for maintaining Cmin,ss >200 ng/mL to suppress pRB/topo IIα and cell cycle progression. Whether this particular prediction of the referenced PK/PD model is supported also by observed data is not obvious.

  IHC of pRB/topo IIα were performed on skin biopsies available from a total of 180 patients enrolled in Study JPBA. The skin biopsies were collected prior to treatment initiation, as well as immediately predose and 4 hours postdose on Day 15 of Cycle 1.



  The skin biopsy data for pRB is very variable, but does perhaps lend some support to the threshold of 200 ng/mL.

- A daily dose of 225 mg achieved mean Cmin,ss of 54.7 ng/mL In order to achieve higher abemaciclib concentrations, a Q12H dosage regimen (75 mg to 275 mg) was subsequently tested, and at the MTD was identified as 200 mg Q12H (Cmin,ss 197 ng/mL). This rational for a two-dose regimen is not understood; the few patients assessed at 225 mg Q24H (n=3) and the PK of 150 mg Q24H suggests a chance finding. This is not pursued further as only Q12H dosing was investigated in confirmatory trials.
- During the dose-escalation phase of the study, 2 of the 3 patients who received abemaciclib 275 mg Q12H experienced DLTs of Grade 3 fatigue. At the next lower dose level (abemaciclib 200 mg Q12H), only 1 of 7 patients experienced a DLT. Therefore, the MTD of the study was set at 200 mg Q12H. This was the dose used in MONARCH-2 prior to protocol amendment a, where the dose was reduced to 150 mg Q12H due to diarrhea causing dose reductions during cycle 1.

Antitumor activity

All efficacy analyses were performed on the 192 patients in the dose-confirmation phase (Parts B, C, D, E, F, and G) who had received at least 1 dose of abemaciclib.

Group	**N**	**Response rate**	**DCR**	**DoR (months)**	**PFS (months)**
NSCLC	68	2.9%	49%	7.5	2.0
GBM	17	0%	18%	-	1.1
Breast cancer	47	23%	70%	13	5.8
HR+	36	31%	81%		
HR-	9	0%	33%		
Melanoma	26	3.8%	27%	5.5	2.0
CRC	15	0%	13%	-	1.9
+ fulvestrant, HR+ breast cancer	19	21%	79%	1.9 – 5.1	8.8

I3Y-MC-JPBC

In this study, 3 dose levels were investigated (100, 150, and 200 mg administered every 12 hours [Q12H]) in Japanese patients with advanced cancer. Dose escalation proceeded, in cohorts of 3 to 6 patients, based on the frequency of dose-limiting toxicities (DLTs) observed in Cycle 1 until either ≥33% of patients in 1 cohort experienced DLT or the planned highest dose level was reached.

Results

The numbers of patients exposed to different doses in the respective parts of the study are tabulated in section 3.3.

- One patient in 6 (16.7%) at 200 mg Q12H experienced DLT of nausea (Grade 2; upgraded to 3 and considered to be a DLT) during Cycle 1, which required a dose omission of more than 25% of the planned dose.

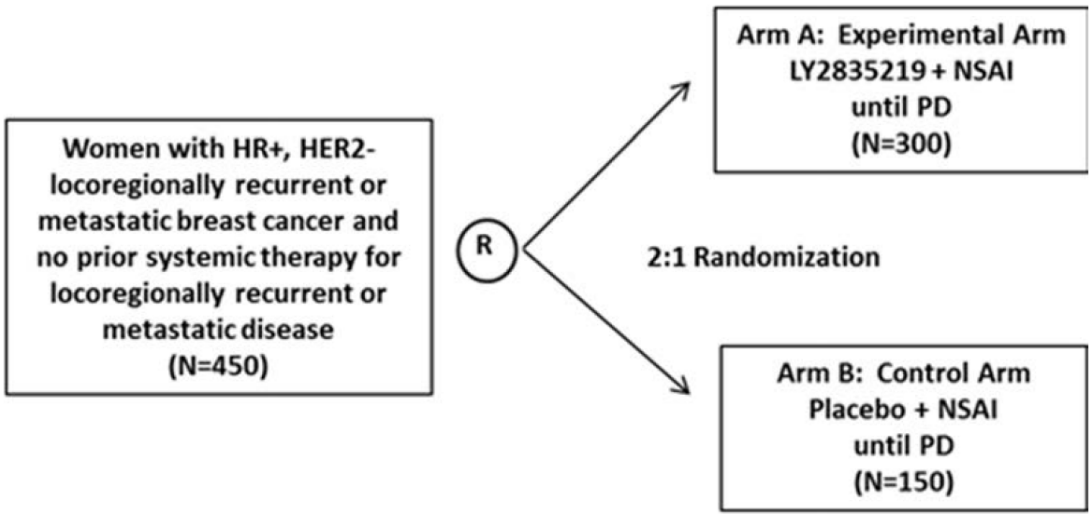
- PK data derived from few patients, and high exposures (600-800 ng/mL) at steady state for doses 100 mg and 150 mg Q12H are considered chance findings with high exposures for one individual in each group.
- As in JPBA, pRB by IHC in skin biposies tends to be lower at day 15. Acknowledging the limitation in numbers.
- There were no responses (CR or PR) observed in Study JPBC. In the 200 mg Q12H cohort, 1 patient was observed to have SD for a disease control rate of 16.7% and 5 patients experienced PFS events with a median of 1.6 months.

2.9.2. Main study(ies)

MONARCH 3 (I3Y-MC-JPBM)

A randomized, double-blind, placebo-controlled, phase 3 study of nonsteroidal aromatase inhibitors (anastrozole or letrozole) plus LY2835219, a CDK4/6 inhibitor, or placebo in postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting.

Study design



NSAI = non-steroidal aromatase inhibitor, PD = progressive disease

Treatments

- Experimental Arm A: abemaciclib 150 mg orally Q12H on Days 1 to 28 plus either letrozole 2.5 mg or anastrozole 1 mg once daily of a 28-day cycle
- Control Arm B: placebo orally Q12H on Days 1 to 28 plus either letrozole 2.5 mg or anastrozole 1 mg once daily of a 28-day cycle

Study participants

Key inclusion criteria:

- Female, ≥ 18 years, ECOG ≤ 1, postmenopausal (age ≥ 60 *or*; age ≤ 60, amenorrhea and FSH + estradiol in postmenopausal range *or*; bilateral oophorectomy).
- Positive for ER and/or PgR by immunohistochemistry (IHC) according to ASCO guidelines (Hammond et.al 2013).
- Not positive for HER2 by IHC or in-situ hybridization according to ASCO guidelines (Wolff et.al 2013).
- Locoregional or metastatic disease not amenable to curative surgery.
- By RECIST 1.1: measurable *or* non-measurable bone-only disease.

Key exclusion criteria:

- Previous endocrine therapy for locoregionally recurrent or metastatic disease. Previous (neo) adjuvant therapy accepted if disease-free interval > 12 months.
- Previous chemotherapy for locoregionally recurrent or metastatic disease. Previous (neo) adjuvant therapy accepted.
- Visceral crisis, lymphangitic spread, CNS metastasis, or inflammatory breast cancer.
- Previous everolimus or CDK4/6 inhibitor, initiated bisphosphonates or RANK-L targeted agent <7 days prior to randomization.

Objectives and endpoints

- Primary objective: PFS by investigator

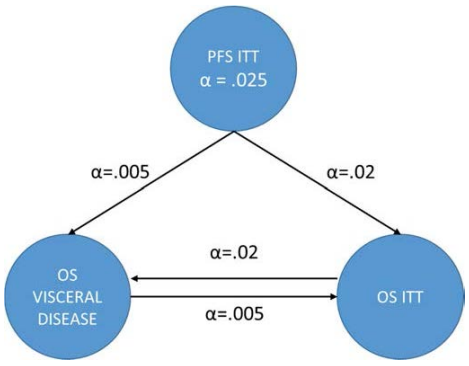
  PFS was censored at date of randomization if baseline or post-baseline assessments were missing (and the patient had not died). Loss to follow-up or withdrawal of consent was censored at date of last adequate tumor assessment, as was progression or death after ≥ 2 missing evaluations.

- Secondary objectives: OS; OS rate at 1, 2 and 3 years; ORR; DoR, disease control rate, clinical benefit rate (CR+PR+SD ≥ 6 months); safety and tolerability; change in symptom burden from baseline by EORTC QLQ-C30, EORTC QLQ-BR23 (breast) and EQ-5D-5L; the PK of abemaciclib, its metabolites, and NSAI therapy.
- Exploratory objective: to explore change in tumor size.

The Applicant should a provide timeline when biomarkers analyses (exploratory objectives) will be available.

Two PFS analyses (after 189 and 240 PFS events) and five OS analyses (also after 189 and 252 OS events, final after ≥ 315 OS events and ≥ 189 OS events in visceral disease patients) were planned.

The graphical method of Maurer and Bretz (2013) to control the overall type I error rate at 0.025 (one-sided) or equivalently, 0.05 (two-sided) was used:



Test	Node α at Analysis	Nominal Significance Level				
		Interim PFS Analysis	Final PFS Analysis	189 OS events	252 OS events	Final OS analysis
1. Initial Graph						
PFS	0.025	0.00025	.0249993	n/a	n/a	n/a
2. Graph following signficant PFS result						
VIS OS	0.005	1*10^-9	3*10^-7	.0003	.0016	.0045
ITT OS	0.020	2*10^-9	2*10^-5	.0027	.0085	.0171
3. Graph following significant PFS and VIS OS result						
ITT OS	0.025	7*10^-9	4*10^-5	.0038	.0110	.0211
4. Graph following significant PFS and ITT OS result						
VISC OS	0.025	7*10^-9	4*10^-5	.0038	.0110	.0211

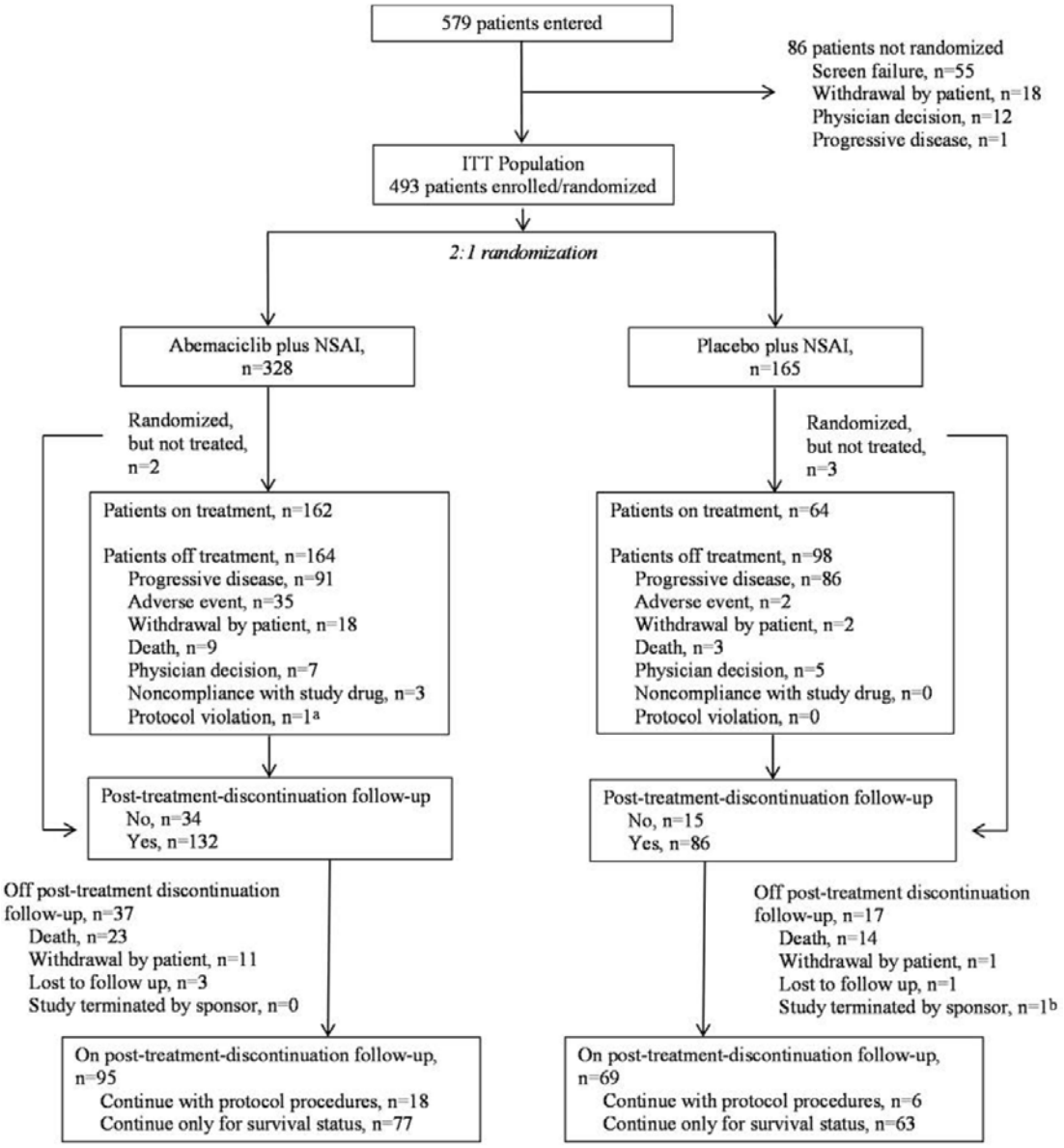
Patients were randomized 2:1 and randomization was stratified by nature of disease (visceral metastases vs bone-only metastases vs other) and prior (neo-) adjuvant endocrine therapy (AI vs other vs none).

Recruitment and patient disposition

A total of 579 patients entered the study (signed the ICF) at 158 sites in 22 countries.

European patients amounted to 53%, Asian to 29%, and North American to 18%.

The first patient was enrolled 18 November 2014, the last in November 2015, data cutoff date for the interim analysis was 31 January 2017. The final PFS analysis with a data cutoff date 3 November 2017 was also provided.



Baseline data

Baseline demographic characteristics, including age, race, ethnicity, region, and ECOG performance status were balanced.

All 493 enrolled patients were female, and the majority were Caucasian (58%) or Asian (30%). The median age was 63 years (range: 32 to 88 years), 60% had a baseline ECOG PS of 0, and 40% had a baseline ECOG PS of 1.

Baseline disease characteristics, including time since diagnosis, histology, disease stage, histopathological grade, HR- and HER2 status were balanced.

Four-hundred and ninety-two patients (99.8%) had HR+ disease, including 77% with ER+/PgR+ disease, 22% with ER+/PgR- disease, 0.8% with ER+/PgR unknown, and 0.4% with ER-/PgR+. A total of 492 patients (99.8%) had HER2- disease.

For patients in both treatment arms, ER, PgR, and HER2 receptor status was mainly derived from the patients' primary tumor tissue (approximately 60% for primary tumor tissue, 40% for metastatic tumor tissue).

Prior therapy & disease setting	Abemaciclib + NSAI N=328 n (%)	Placebo + NSAI N=165 n (%)	Total N=493 n (%)
Neoadjuvant therapy			
Chemotherapy	23 (7.0%)	17 (10%)	40 (8.1%)
Endocrine	2 (0.6%)	7 (4.2%)	9 (1.8%)
Curative intent surgery	201 (61%)	102 (62%)	303 (62%)
Adjuvant therapy			
Chemotherapy	114 (35%)	54 (33%)	168 (34%)
Endocrine	140 (43%)	72 (44%)	212 (43%)
Recurrent disease			
Locoregionally	11 (3.4%)	5 (3.0%)	16 (3.2%)
Metastatic	182 (56%)	99 (60%)	281 (57%)
De novo metastatic disease	135 (41%)	61 (37%)	196 (40%)
Nature of disease			
Visceral disease	172 (52%)	89 (54%)	261 (53%)
Bone-only disease	70 (21%)	39 (24%)	109 (22%)
Other (breast, nodal, skin, soft tissue)	86 (26%)	37 (22%)	123 (25%)

Results

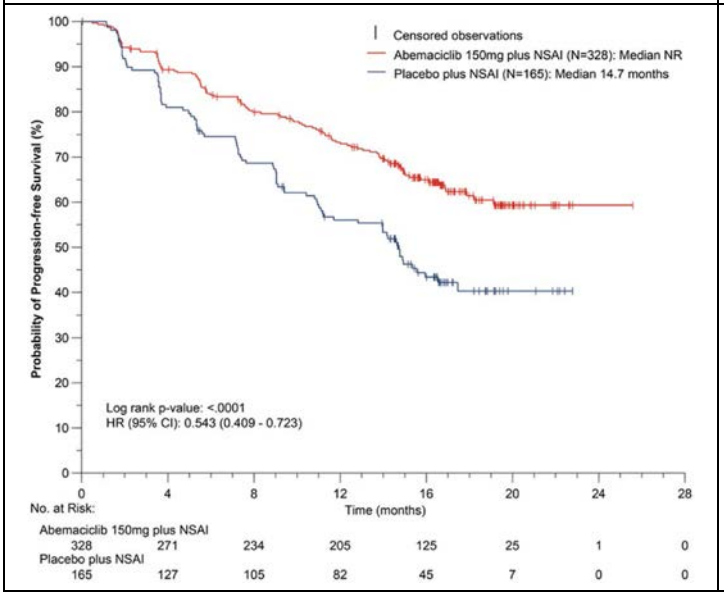
Primary endpoint – progression-free survival, 31 Jan 2017

The primary endpoint PFS by investigator was met, with a p-value < the 0.00025 specified for the first interim PFS analysis:

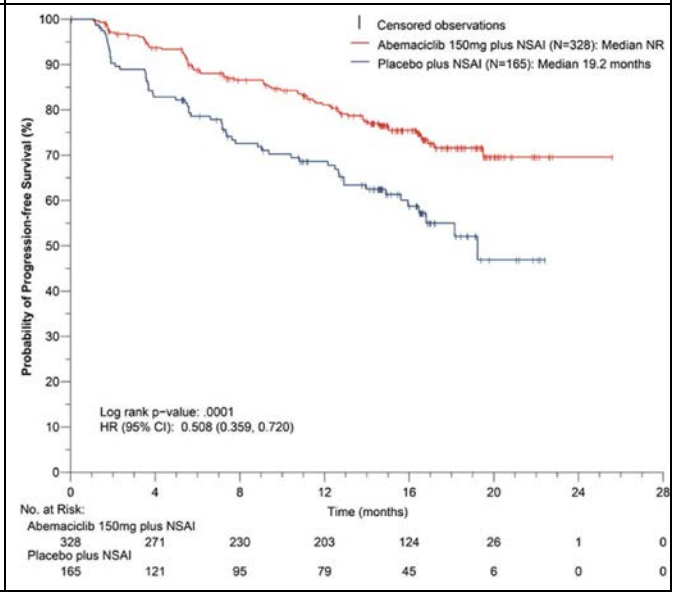
Analysis	Events		Censored, assessments:					HR (p)
	PD	Death	≥ 2 missed	No baseline	No post baseline	Regular, no PD	New cancer therapy	
PFS by investigator								
Abemaciclib + NSAI (n=328)	97	11	4	2	8	206	-	0.54 (0.000021)
Placebo + NSAI (=165)	82	4	1	1	5	72	-	
PFS by independent review								
Abemaciclib + NSAI (n=328)	60	12	8	4	9	235	-	0.51 (0.0001)
Placebo + NSAI (=165)	55	4	1	2	6	97	-	
PFS censored for new anticancer therapy								
Abemaciclib + NSAI (n=328)	89	11	4	2	8	191	23	0.54 (<.0001)
Placebo + NSAI (=165)	79	3	1	1	5	70	6	
Updated PFS new anticancer	107	17	3	0	7	148	46	0.61

therapy as event								(.000042)
Abemaciclib + NSAI (n=328)								
Placebo + NSAI (=165)	102	3	1	1	3	37	18	
PFS nonobjective progression								
Abemaciclib + NSAI (n=328)	106	11	5	-	8	198	-	0.56 (<.0001)
Placebo + NSAI (=165)	87	4	1	-	6	67	-	
PFS forwarded if (unscheduled)								
Abemaciclib + NSAI (n=328)	73 (24)	11	4	2	8	206	-	0.54 (<.0001)
Placebo + NSAI (=165)	61 (21)	4	1	1	5	72	-	
PFS adjusted for prognostic factors (bone / visceral / other and geographic region)								0.54 (<.0001)
Abemaciclib + NSAI (n=328)	97	11	4	2	8	206	-	
Placebo + NSAI (=165)	82	4	1	1	5	72	-	

PFS by investigator



PFS by independent review

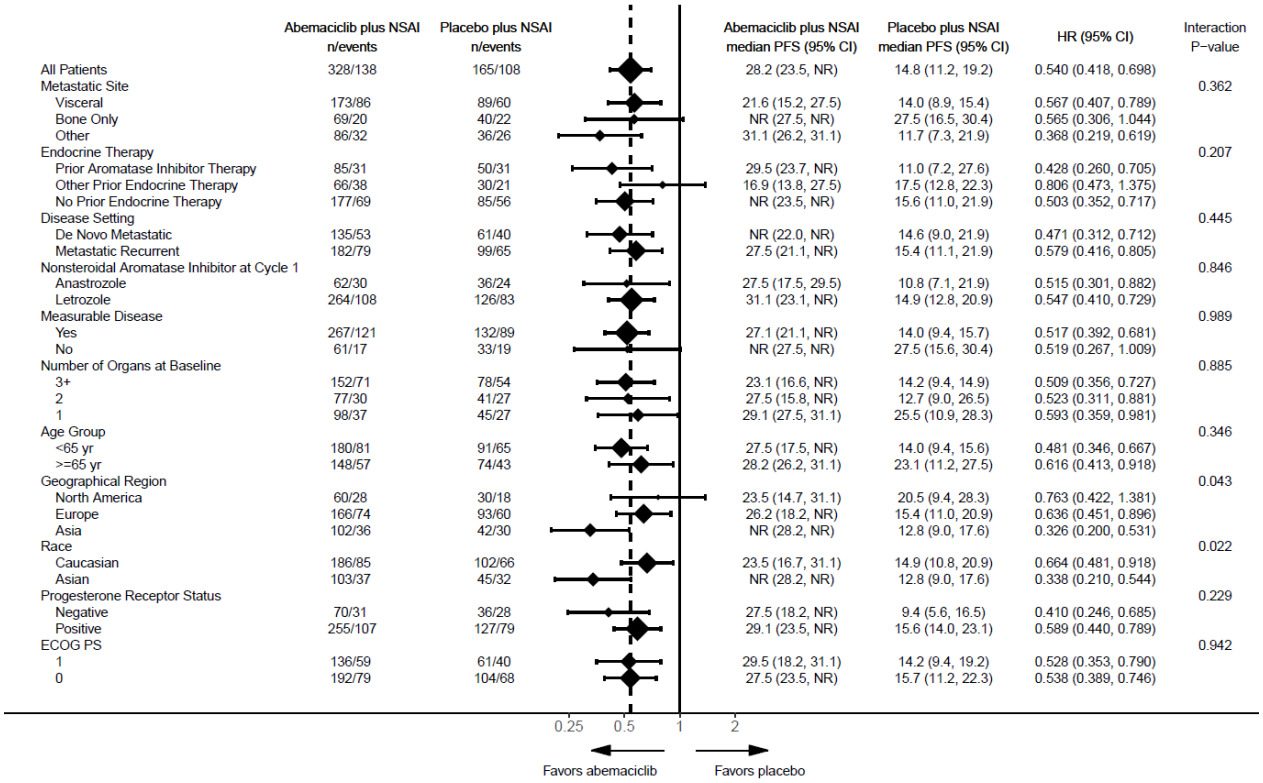


The investigator-to-independent review discordance in progression calls was large; the reason may become clearer if the anatomical site of progression is investigated.

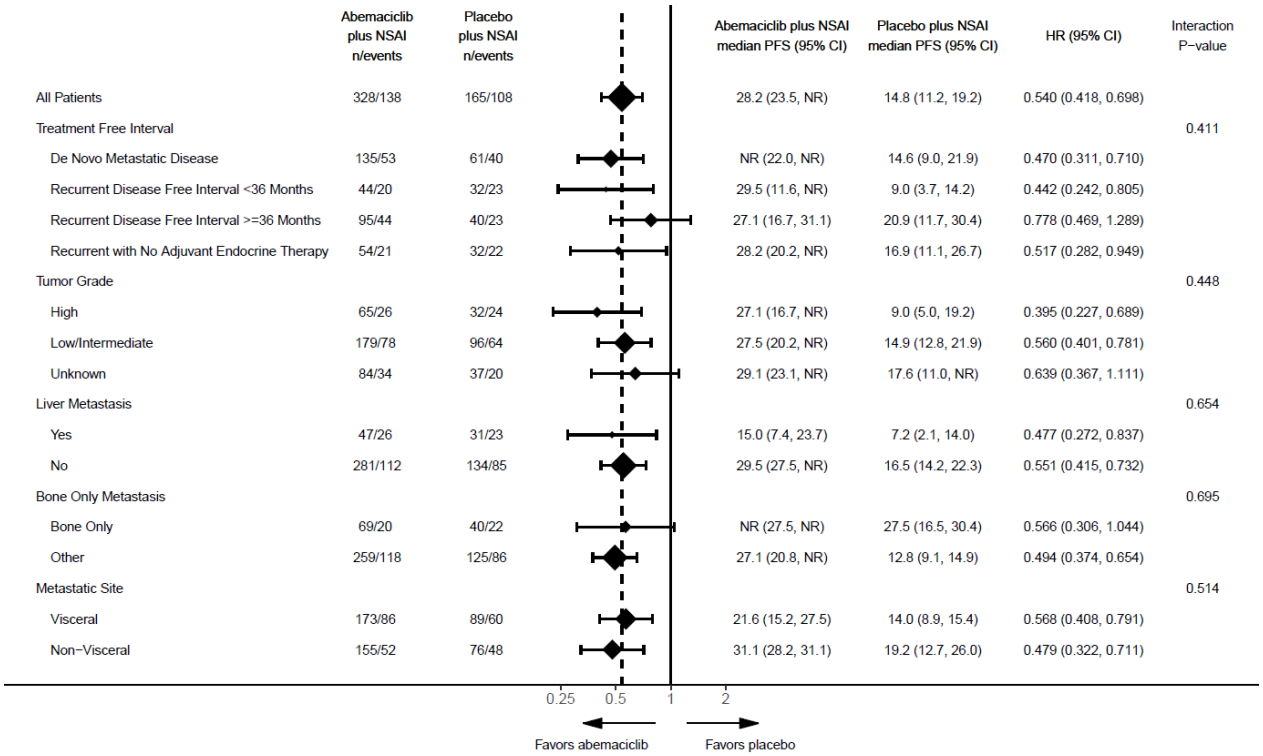
Updated and final PFS analysis, 3 Nov 2017

With 9 months of additional follow-up, a final investigator PFS analysis was made according to plan after 246 events (50%), 138 (42%) in the experimental vs. 108 (66%) in the control arm. The medians were 28 vs. 15 months, HR 0.54, p= 0.000002. Results were consistent with independent review (NR vs. 19 months, HR 0.46) and the interim (primary) PFS analysis.

Forest plot of summary of progression-free survival by preplanned subgroups, intent-to-treat population – MONARCH3 final PFS cutoff.

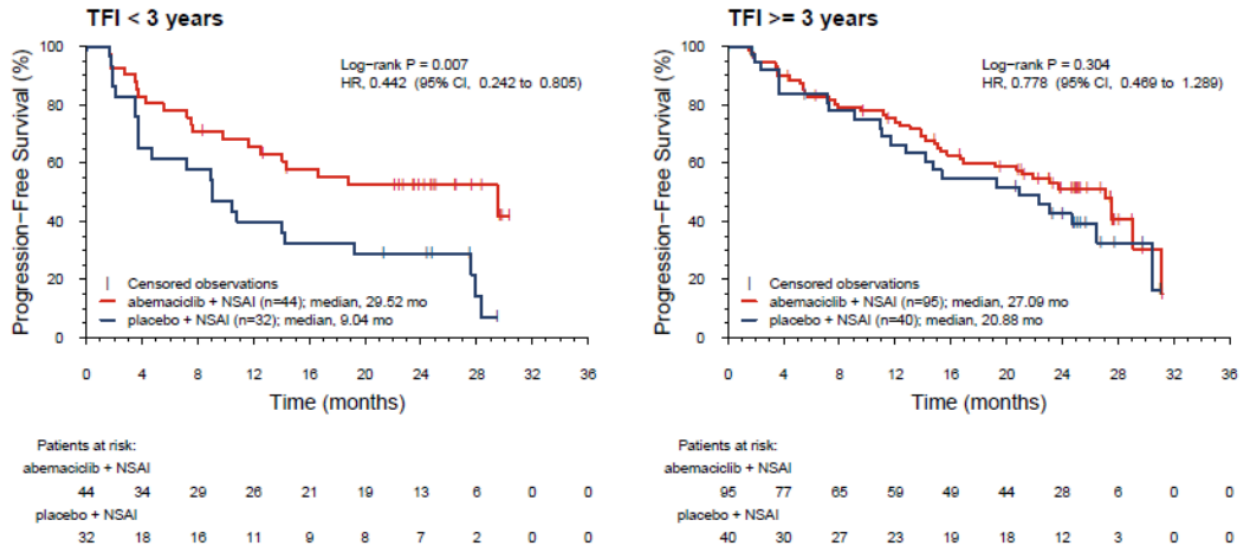


Forest plot of summary of progression-free survival by additional subgroups of interest, intent-to-treat population – MONARCH 3 final PFS cutoff.



Among the exploratory subgroups, a more limited benefit was noted from the combination treatment for patients with longer DFI (≥36 months). A prolonged treatment-free interval is considered a predictor of response to hormone therapy (Johnston, 2010), hypothetically explaining a lack of benefit from the addition of abemaciclib. Patients with DFI ≥36 months and < 36 months were further divided into subgroups on the basis of whether the diagnosis was made in primary or metastatic tissue, with the hypothesis that primary tissue may become less relevant with time, but results were inconclusive due to small numbers.

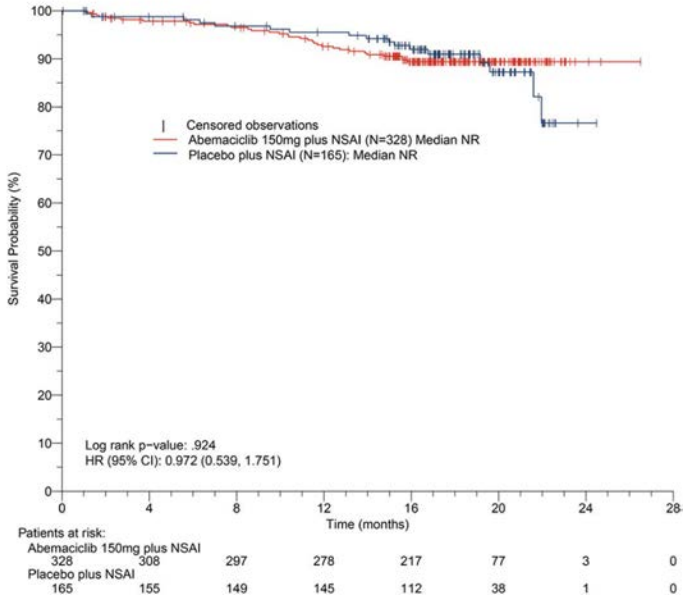
MONARCH 3 Kaplan-Meier plot of PFS according to recurrent treatmentfree interval



Secondary endpoint – overall survival

The secondary endpoints OS in the ITT and OS in the visceral disease populations, with specified p-values in the 10^{-9} range, were not met:

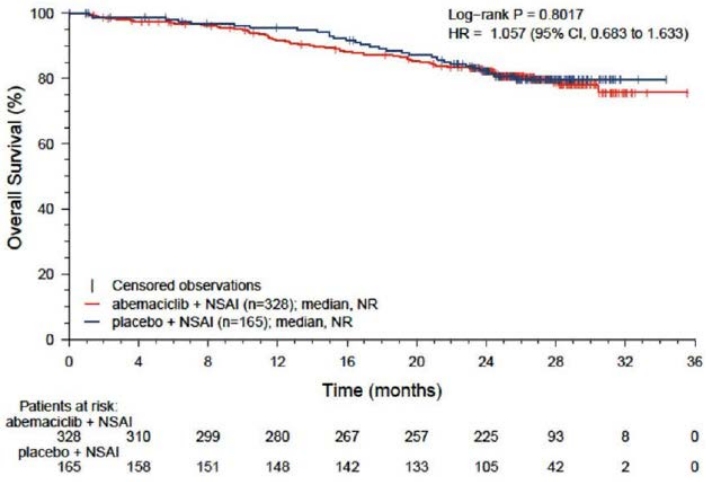
	ITT	
	Abemaciclib + NSAI (n=328)	Placebo + NSAI (=165)
Deaths, n (%)	32 (9.8)	17 (10)
Censored, n (%)	296 (90)	148 (90)
Alive	290	147
Lost to follow-up	3	1
Patient withdrawal	3	0
Hazard ratio	0.97	
p-value	0.92	



Updated OS analysis, 3 Nov 2017

An updated OS analysis was performed, as planned, in conjunction with the final PFS analysis. The event rate had increased to 93 (19%), with 63 (19%) in the experimental and 30 (18%) in the control arm, HR 1.06, p= 0.80:

	ITT	
	Abemaciclib + NSAI (n=328)	Placebo + NSAI (=165)
Deaths, n (%)	63 (19)	30 (18)
Censored, n (%)	265 (81)	135 (82)
Alive	261	135
Lost to follow-up	1	0
Patient withdrawal	3	0
Hazard ratio	1.06	
p-value	0.80	

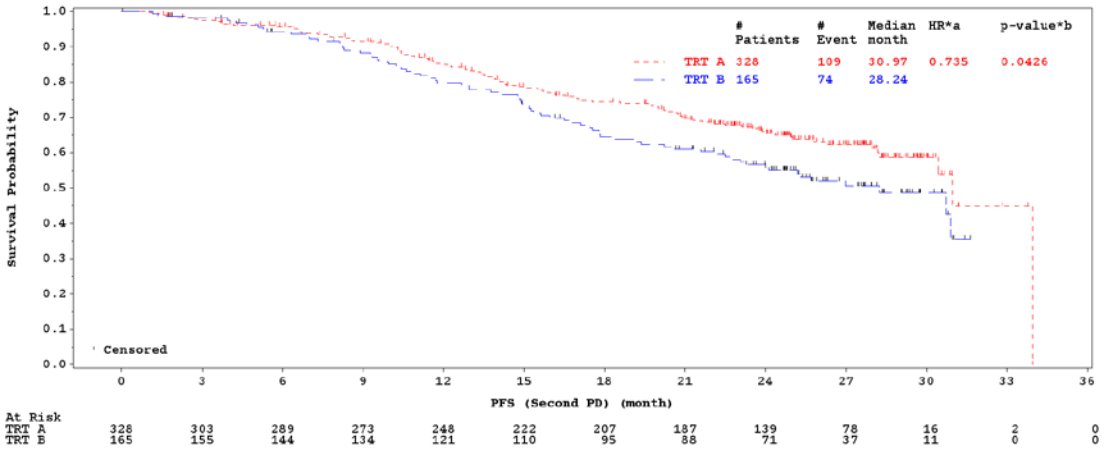


Time to Second Disease Progression

The second objective disease progression date was not collected in the MONARCH 3 trial. Therefore, the second objective disease progression date was replaced with the discontinuation date of next line (first line of post discontinuation) treatment or starting date of the second line of post-discontinuation treatment, whichever was earlier.

Summary of Time to Second Disease Progression Intent-to-Treat Population MONARCH 3

	Abemaciclib + NSAI N=328	Placebo + NSAI N=165	Treatment Effect/Difference/ p-Value[c]
Number of events, n (%)	109 (33.2)	74 (44.8)	
Death without second PD	35 (10.7)	12 (7.3)	
Second PD	74 (22.6)	62 (37.6)	
Number of patients censored, n (%)	219 (66.8)	91 (55.2)	
No baseline tumour assessment	1 (0.3)	1 (0.6)	
No postbaseline tumour assessment	9 (2.7)	4 (2.4)	
No documented PD with regular assessment	174 (53.0)	46 (27.9)	
No documented second PD/death after initial PD	35 (10.7)	40 (24.2)	
Median (95% CI) months	31.0 (30.4, 34.0)	28.2 (22.7, NR)	2.73
p-Value (2-sided) log rank stratified			.0426
Hazard ratio (95% CI) – stratified[b]			0.735 (0.545, 0.991)



Secondary endpoints – best overall response (BOR), overall response rate (ORR), disease control rate (DCR) and clinical benefit rate (CBR)

	Abemaciclib + NSAI N=328		Placebo + NSAI N=165		Unstratified Odds Ratio	p-Value[c]
Best Overall Response[a]	n (%)	95% CI[b]	n (%)	95% CI[b]		
Complete response (CR)	9 (2.7)	1.0, 4.5	1 (0.6)	-0.6, 1.8		
Partial response (PR)	154 (47.0)	41.6, 52.4	60 (36.4)	29.0, 43.7		
Stable disease (SD)	128 (39.0)	33.7, 44.3	82 (49.7)	42.1, 57.3		
≥6 months	93 (28.4)	23.5, 33.2	57 (34.5)	27.3, 41.8		
Progressive disease (PD)	12 (3.7)	1.6, 5.7	12 (7.3)	3.3, 11.2		
Not evaluable[d]	25 (7.6)	4.8, 10.5	10 (6.1)	2.4, 9.7		
Overall response rate (CR + PR)	163 (49.7)	44.3, 55.1	61 (37.0)	29.6, 44.3	1.684	.005
Disease control rate (CR + PR + SD)	291 (88.7)	85.3, 92.1	143 (86.7)	81.5, 91.9	1.210	.501
Clinical benefit rate (CR + PR + SD ≥6 months)	256 (78.0)	73.6, 82.5	118 (71.5)	64.6, 78.4	1.416	.101

Secondary endpoints for patients with measurable disease[a] – overall response rate (ORR) and clinical benefit rate (CBR)

	Abemaciclib + NSAI	Placebo + NSAI
Objective response (measurable disease)	**N=328**	**N=165**
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.

Secondary endpoints – EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L

EORTC QLQ-C30:

Most of the differences between arms (13 of 15) did not reach the threshold to be considered a small improvement or a small deterioration.

	Baseline score		**Change from baseline**			
	Abemaciclib + NSAI	Placebo + NSAI	Abemaciclib + NSAI	Placebo + NSAI	**Difference**	**p-value**
Global health status	65	59	-0.03	4.3	-4.4	.003
Fatigue	32	38	2.4	-2.6	5.0	.004
Nausea and vomiting	7.2	8.1	2.4	-0.36	2.8	.013
Appetite loss	18	22	0.15	-3.9	4.0	.034
Diarrhea	8.3	7.3	18.2	-0.5	18.7	<.001

In the abemaciclib plus NSAI arm, diarrhea showed at least a medium difference from the placebo plus NSAI arm. Global health status in the placebo plus NSAI arm showed a small improvement. There were between-group significant difference for fatigue, nausea/vomiting, and appetite loss; however, this did not reach the threshold described by Cocks et al. 2011.

EORTC QLQ-BR23**:**

	Baseline score		**Change from baseline**			
	Abemaciclib + NSAI	Placebo + NSAI	Abemaciclib + NSAI	Placebo + NSAI	**Difference**	**p-value**
Body image	82	80	-4.5	0.6	-5.1	.009
Systemic therapy side effects	16	18	8.2	3.7	4.5	<.001

In the analysis of all post-baseline visits by treatment arm, no clinically relevant (>5 points; Sprangers et al. 1996) between-group differences were observed for the QLQ-BR23 functional and symptom scales.

EQ-5D-5L:

Table JPBM.7.13. Key Summary of EQ-5D-5L Index and VAS by Visit
Safety Population Final PFS Database Lock

	Baseline Score Mean (Std Dev)		Change from Baseline[a] LS Mean (SE)		Change Difference (Abemaciclib – Placebo)[a] LS Mean (SE)	p-Value[b]
	Abemaciclib + NSAI	Placebo + NSAI	Abemaciclib + NSAI	Placebo + NSAI		
Index value	0.72 (0.22)	0.69 (0.21)	0.01 (0.01)	0.01 (0.01)	-0.01 (0.02)	0.688
Visual analog scale	70.89 (19.26)	69.65 (19.45)	0.49 (0.78)	1.51 (1.15)	-1.01 (1.39)	0.466

The EQ-5D-5L index values across all post-baseline visits were stable and similar between arms.

Summary of efficacy for trial MONARCH 3

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219 (abemaciclib), a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting			
Study identifier	I3Y-MC-JPBM (MONARCH 3)		
Design	Phase 3, randomized (2:1), double blind, placebo-controlled, multicentre trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		study ongoing not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Abemaciclib plus NSAI		Abemaciclib 150 mg orally twice a day, plus either letrozole 2.5 mg or anastrozole 1 mg once daily of a 28-day cycle. Treatment until PD or other discontinuation criteria were fulfilled. 328 pts randomized.
	Placebo plus NSAI		Placebo orally twice a day, plus either letrozole 2.5 mg or anastrozole 1 mg once daily of a 28-day cycle. Treatment until PD or other discontinuation criteria were fulfilled. 165 pts randomized.
Endpoints and definitions	Primary endpoint	PFS	By investigator according to RECIST 1.1. Time from the date of randomization to the date of objective progression or the date of death due to any cause, whichever was earlier.
	(Gated) secondary endpoint	OS	Time from the date of randomization to the date of death from any cause.

	Secondary endpoints	OS at 1, 2, and 3 years; ORR (CR+PR) (per RECIST 1.1 by investigator); duration of response (DoR); disease control rate (DCR =CR+PR+SD); clinical benefit rate (CBR= CR + PR + SD ≥ 6 months); change in symptom burden from baseline
Database lock	Database lock: 5 April 2017	

Results and Analysis

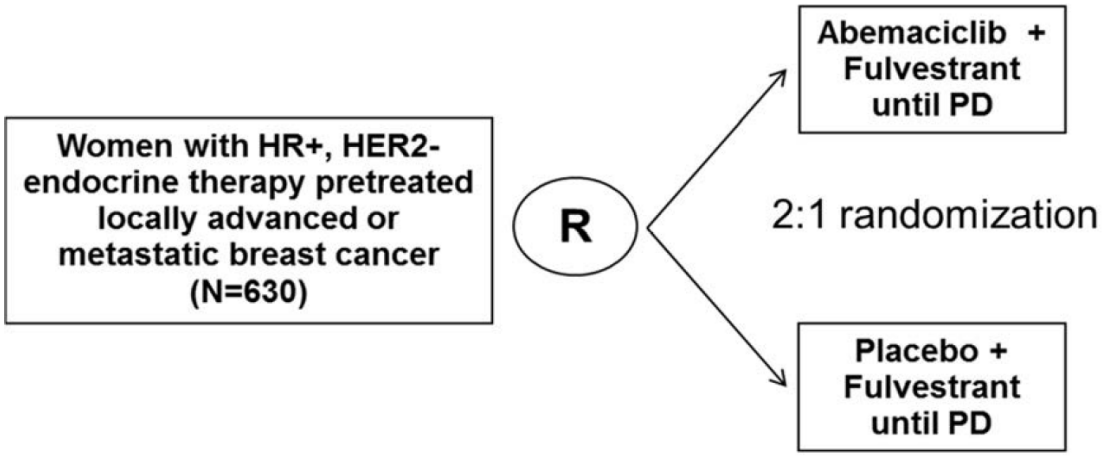
Analysis description	**Interim and Final Analysis**		
Analysis population and time point description	Intent to treat (493 patients) Data cut-off for the interim analysis of PFS: 31 January 2017 Data cut-off for the final analysis of PFS: 3 November 2017		
Descriptive statistics and estimate variability; Effect estimate per comparison	Treatment group	Abemaciclib plus NSAI	Placebo plus NSAI
	Number of subject	328	165
	Primary endpoint		
	Interim PFS N. with events (%)	108 (32.9%)	86 (52.1%)
	Median PFS months (95% CI)	NR (NR, NR)	14.7 (11.1, 17.5)
	HR (95% CI) p-value (2-sided log rank stratified)	0.543 (0.409, 0.723) p= 0.000021	
	Updated PFS N. with events (%)	138 (42.1%)	108 (65.5%)
	Median PFS months (95% CI)	28.2 (23.5, NR)	14.8 (11.2, 19.2)
	HR (95% CI) p-value (2-sided log rank stratified)	0.540 (0.418, 0.0.698) p= 0.000002	
	Secondary endpoints		
	Interim OS N. with events (%)	32 (9.8%)	17 (10.3%)
	Median OS months (95% CI)	NR (NR, NR)	NR (NR, NR)
	HR (95% CI) p-value (2-sided log rank stratified)	0.972 (0.539, 1.751) p= 0.9242	
	Updated OS N. with events (%)	63 (19.2%)	30 (18.2%)
	Median OS months (95% CI)	NR (NR, NR)	NR (NR, NR)
	HR (95% CI) p-value (2-sided log rank stratified)	1.057 (0.683, 1.633) p= 0.8017	

	Updated ORR (95% CI)	49.7% (44.3, 55.1)	37.0% (29.6, 44.3)
	OR unstratified (95% CI) p-value	1.7 p=0.005	
	Updated DoR median (months) (95%CI)	27.39 (25.74, NR)	17.46 (11.21, 22.19)
	Updated DCR (95% CI)	88.7% (85.3, 92.1)	86.7% (81.5, 91.9)
	OR (95% CI) p-value	1.2 p=0.501	
	Updated CBR (95% CI)	78% (73.6, 82.5)	71.5 (64.6, 78.4)
	OR (95% CI) p-value	1.4 p=0.101	

MONARCH 2 (I3Y-MC-JPBL)

A randomized, double-blind, placebo-controlled, phase 3 study of fulvestrant with or without abemaciclib, a CDK4/6 inhibitor, for women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer.

Study design



PD= progressive disease

Treatments

- Experimental Arm A: abemaciclib 150 mg orally Q12H on Days 1 to 28 of a 28-day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.
- Control (Placebo) Arm B: placebo orally Q12H on Days 1 to 28 of a 28-day cycle plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond.

Study participants

Key inclusion criteria

- Female, ≥ 18 years, ECOG ≤ 1, postmenopausal status due to a GnRH agonist or natural/surgical causes (age ≥ 60 *or*; age ≤ 60, amenorrhea and FSH + estradiol in postmenopausal range *or*; bilateral oophorectomy).
- Positive for ER and/or PgR by immunohistochemistry (IHC) according to ASCO guidelines (Hammond et.al 2013).
- Not positive for HER2 by IHC or in-situ hybridization according to ASCO guidelines (Wolff et.al 2013).
- Locoregional or metastatic disease not amenable to curative surgery.
- Relapse/progression while receiving or within 1 year of completing (neo) adjuvant endocrine therapy, no subsequent endocrine therapy.
- Relapse after 1st line metastatic treatment with an anti-estrogen or aromatase inhibitor, no chemotherapy in the metastatic setting.
- By RECIST 1.1: measurable *or* non-measurable bone-only disease.

Key exclusion criteria

- Visceral crisis, lymphangitic spread, CNS metastasis, or inflammatory breast cancer.
- Previous non- (neo) adjuvant chemotherapy, fulvestrant, everolimus or CDK4/6 inhibitor, initiated bisphosphonates or RANK-L targeted agent <7 days prior to randomization.

The Applicant should clarify whether there were patients who started with bone-modifying agents while study treatment was ongoing.

Objectives and endpoints

- Primary objective: PFS by investigator

  PFS was censored at date of randomization if baseline or post-baseline assessments were missing (and the patient had not died). Loss to follow-up or withdrawal of consent was censored at date of last adequate tumor assessment, as was progression or death after ≥ 2 missing evaluations.

- Secondary objectives: OS; OS rate at 1, 2 and 3 years; ORR; DoR, disease control rate, clinical benefit rate (CR+PR+SD ≥ 6 months); safety and tolerability; pain and symptom burden using the Brief Pain Inventory (BPI), EORTC QLQ-C30 and EORTC QLQ-BR23 (breast) questionnaires, EQ-5D 5L; the PK of abemaciclib, its metabolites, and fulvestrant.

Two PFS analyses (after 265 and 378 PFS events) and four OS analyses (also after 331 and 441 OS events) were planned.

To control the type I error rate at a one sided p of 0.025, the p-value of 0.00001 was specified for the interim PFS analysis, with alpha 0.2499996 remaining for the final PFS analysis. OS was to be controlled hierarchically, with alpha-spending between the respective OS analyses determined by an O'Brien-Fleming type stopping boundary.

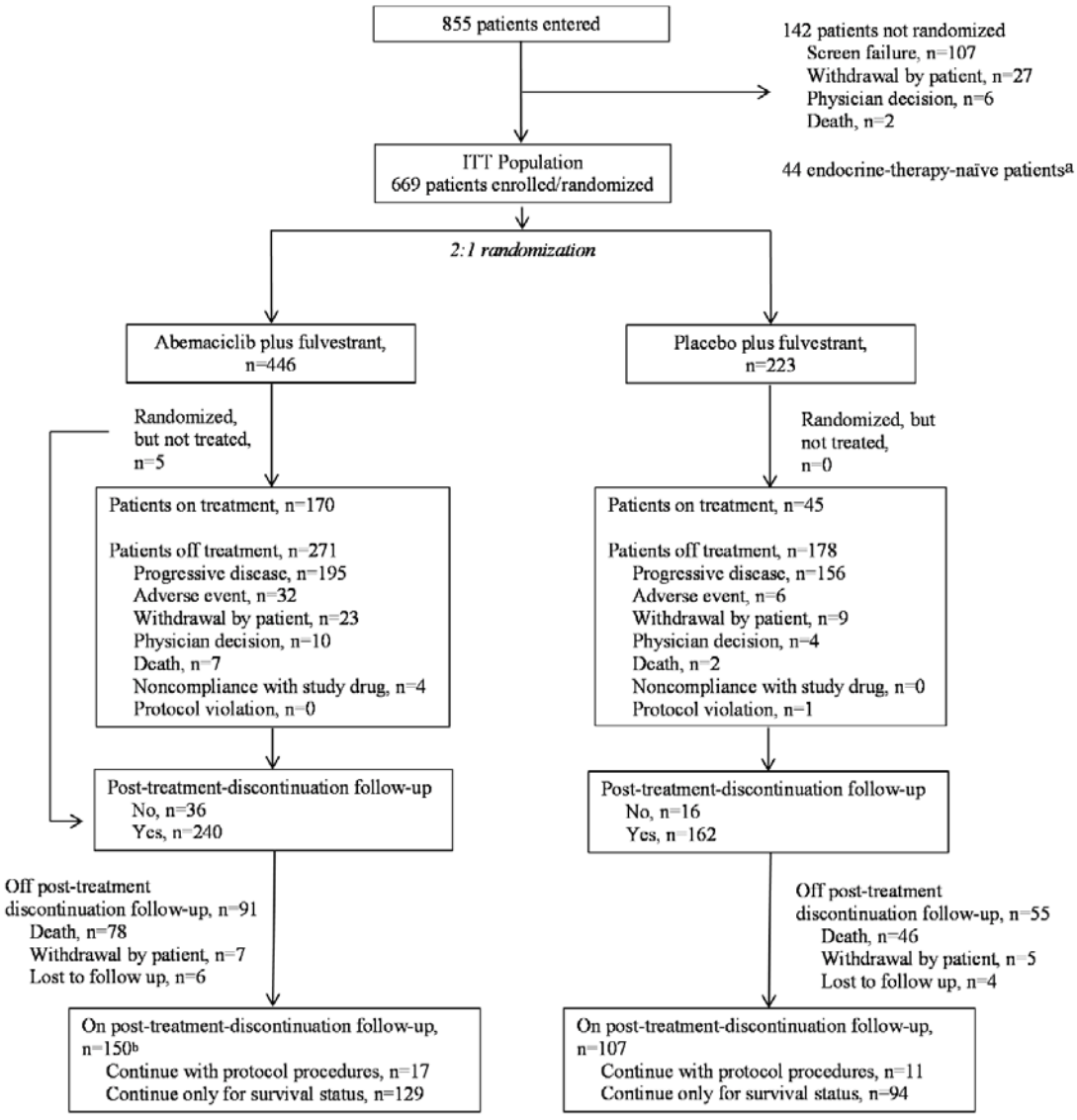
Patients were randomized using the following stratification factors: nature of disease (visceral metastases vs bone-only metastases vs other) and sensitivity to endocrine therapy (primary resistance vs secondary

resistance, i.e. progression within 2 years of adjuvant treatment or within 6 months of advanced treatment defining primary resistance vs. not fulfilling these criteria).

Recruitment and patient disposition

A total of 855 patients entered the study (signed the ICF) at 145 sites in 19 countries. The geographic distribution of patients was Europe 42%, Asia 32%, North America 27%.

The first patient was enrolled 7 August 2014; the last patient 29 December 2015, data cutoff was 14 February 2017.



Baseline data

Demographic characteristics were balanced between treatment arms. All 669 enrolled patients were female, and the majority were white (56%) or Asian (32%). The median age was 60 years (range: 32.0 to 91.0 years). Sixty percent of patients had a baseline ECOG PS of 0, 40% a PS of 1. The majority of patients (82%) were postmenopausal. Seventeen percent were pre/peri-menopausal (i.e., received ovarian suppression with a GnRH agonist).

Baseline disease characteristics, including duration of disease, histopathological grade, and stage were balanced. Hormone positivity was a s follows: 75% ER+/PgR+, 21% with ER+/PgR-, and 2.4% with ER+/PgR unknown, and 1.2% with ER-/PgR+.

Prior therapy & disease setting	**Abemaciclib N=446 n (%)**	**Placebo N=223 n (%)**	**Total N=669 n (%)**
Neoadjuvant therapy			
Chemotherapy	75 (17%)	40 (18%)	115 (17%)
Endocrine	26 (5.8%)	11 (4.9%)	37 (5.5%)
Curative intent surgery	331 (74%)	175 (79%)	506 (76%)
Adjuvant therapy			
Chemotherapy	209 (47%)	103 (46%)	312 (47%)
Endocrine	323 (72.4%)	170 (76.2%)	493 (73.7%)
Recurrent disease			
Locally advanced	16 (3.6%)	2 (0.9%)	18 (2.7%)
Metastatic	427 (96%)	221 (99%)	648 (97%)
Nature of disease			
Visceral disease	245 (55%)	128 (57%)	373 (56%)
Bone-only disease	123 (28%)	57 (26%)	180 (27%)
Other (breast, nodal, skin, soft tissue)	75 (17%)	38 (17%)	113 (17%)
Eligibility criteria met, relapse:			
During (neo) adjuvant endocrine therapy	197 (44%)	103 (46%)	300 (45%)
Within 1 year of completed adjuvant endocrine therapy	41 (9.2%)	18 (8.1%)	59 (8.8%)
After 1st advanced line AE or AI, > 1 year TFI from adjuvant treatment	118 (27%)	62 (28%)	180 (27%)
After 1st advanced line AE or AI, de novo metastatic	82 (18%)	36 (16%)	118 (18%)
AE= antioestrogen, AI= aromatase inhibitor, DFI= disease-free interval			

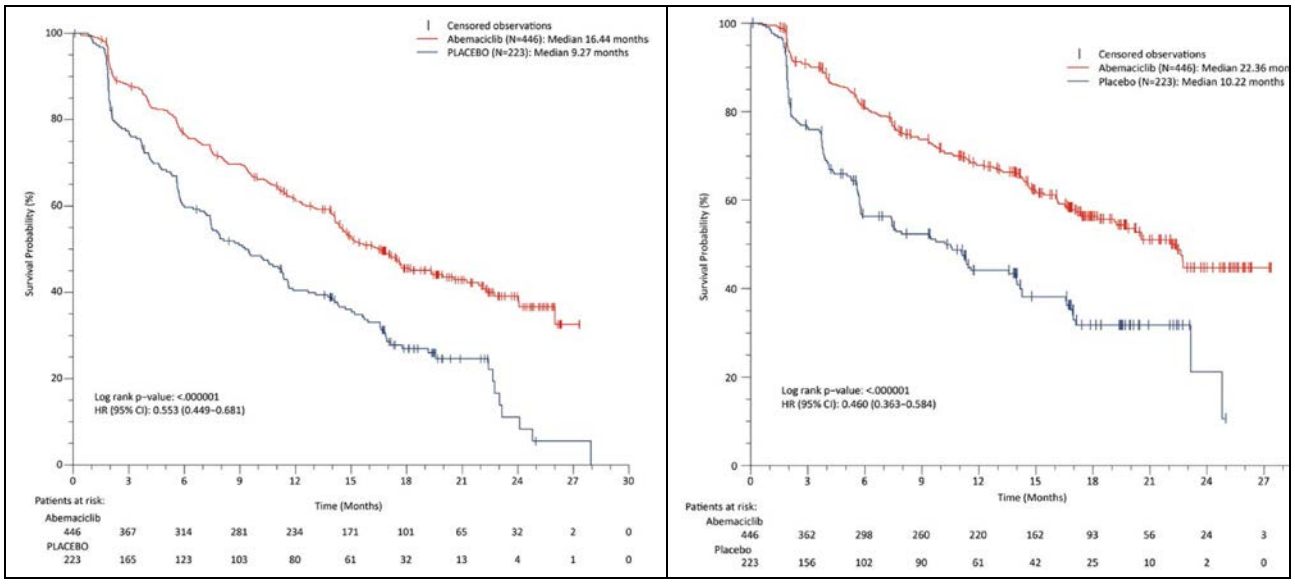
Results

Primary endpoint – progression-free survival

The primary endpoint PFS by investigator was met, with a p-value < the 0.00001 specified for the first interim PFS analysis:

Analysis	Events		Censored, assessments:					HR (p)
	PD	Death	≥ 2 missed	No baseline	No post baseline	Regular, no PD	New cancer therapy	
PFS by investigator								
Abemaciclib (n=446)	211	11	9	3	10	202	-	0.55 (<.0000001)
Placebo (=223)	153	4	2	0	4	60	-	
PFS by independent review Abemaciclib (n=446)	143	21	24	5	10	243	-	0.46 (<.000001)
Placebo (=223)	119	5	4	0	5	90	-	
PFS censored for new anticancer therapy								
Abemaciclib (n=446)	189	9	9	3	10	193	33	0.53 (<.0001)
Placebo (=223)	148	4	2	0	4	57	8	
PFS new anticancer therapy as event								
Abemaciclib (n=446)	192	9	3	3	7	187	45	0.60 (<.000001)
Placebo (=223)	148	4	1	0	4	52	14	
PFS nonobjective progression								
Abemaciclib (n=446)	220	9	10	-	12	195	-	0.54 (<.0001)
Placebo (=223)	162	4	2	-	4	51	-	
PFS forwarded if (unscheduled)								
Abemaciclib (n=446)	141 (70)	11	9	3	10	202	-	0.55 (<.0001)
Placebo (=223)	111 (42)	4	2	0	4	60	-	
PFS adjusted for prognostic factors (bone vs visceral / ECOG 0 vs. 1)								
Abemaciclib (n=446)	211	11	9	3	10	202	-	0.55 (<.0001)
Placebo (=223)	153	4	2	0	4	60	-	

PFS by investigator	**PFS by independent review**

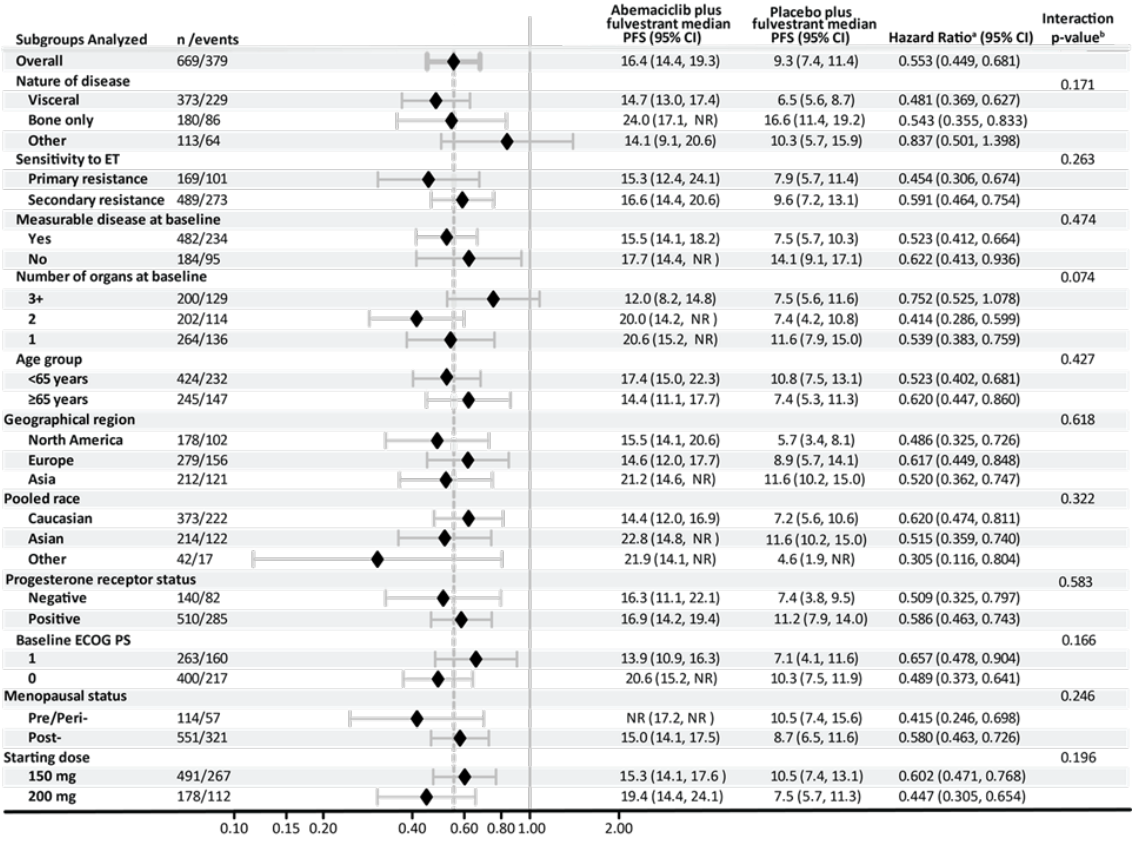


The investigator-to-independent review discordance in progression calls was large. The anatomical sites of progression were investigated and, not unexpectedly, discrepant calls were often the case for skeletal lesions, whereas calls were concordant for liver lesions.

PFS subgroup analyses

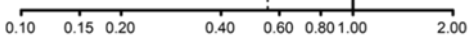
Planned:

Subgroups Analyzed	n /events	Abemaciclib plus fulvestrant median PFS (95% CI)	Placebo plus fulvestrant median PFS (95% CI)	Hazard Ratio[a] (95% CI)	Interaction p-value[b]
Overall	669/379	16.4 (14.4, 19.3)	9.3 (7.4, 11.4)	0.553 (0.449, 0.681)	
Nature of disease					0.171
Visceral	373/229	14.7 (13.0, 17.4)	6.5 (5.6, 8.7)	0.481 (0.369, 0.627)	
Bone only	180/86	24.0 (17.1, NR)	16.6 (11.4, 19.2)	0.543 (0.355, 0.833)	
Other	113/64	14.1 (9.1, 20.6)	10.3 (5.7, 15.9)	0.837 (0.501, 1.398)	
Sensitivity to ET					0.263
Primary resistance	169/101	15.3 (12.4, 24.1)	7.9 (5.7, 11.4)	0.454 (0.306, 0.674)	
Secondary resistance	489/273	16.6 (14.4, 20.6)	9.6 (7.2, 13.1)	0.591 (0.464, 0.754)	
Measurable disease at baseline					0.474
Yes	482/234	15.5 (14.1, 18.2)	7.5 (5.7, 10.3)	0.523 (0.412, 0.664)	
No	184/95	17.7 (14.4, NR)	14.1 (9.1, 17.1)	0.622 (0.413, 0.936)	
Number of organs at baseline					0.074
3+	200/129	12.0 (8.2, 14.8)	7.5 (5.6, 11.6)	0.752 (0.525, 1.078)	
2	202/114	20.0 (14.2, NR)	7.4 (4.2, 10.8)	0.414 (0.286, 0.599)	
1	264/136	20.6 (15.2, NR)	11.6 (7.9, 15.0)	0.539 (0.383, 0.759)	
Age group					0.427
<65 years	424/232	17.4 (15.0, 22.3)	10.8 (7.5, 13.1)	0.523 (0.402, 0.681)	
≥65 years	245/147	14.4 (11.1, 17.7)	7.4 (5.3, 11.3)	0.620 (0.447, 0.860)	
Geographical region					0.618
North America	178/102	15.5 (14.1, 20.6)	5.7 (3.4, 8.1)	0.486 (0.325, 0.726)	
Europe	279/156	14.6 (12.0, 17.7)	8.9 (5.7, 14.1)	0.617 (0.449, 0.848)	
Asia	212/121	21.2 (14.6, NR)	11.6 (10.2, 15.0)	0.520 (0.362, 0.747)	
Pooled race					0.322
Caucasian	373/222	14.4 (12.0, 16.9)	7.2 (5.6, 10.6)	0.620 (0.474, 0.811)	
Asian	214/122	22.8 (14.8, NR)	11.6 (10.2, 15.0)	0.515 (0.359, 0.740)	
Other	42/17	21.9 (14.1, NR)	4.6 (1.9, NR)	0.305 (0.116, 0.804)	
Progesterone receptor status					0.583
Negative	140/82	16.3 (11.1, 22.1)	7.4 (3.8, 9.5)	0.509 (0.325, 0.797)	
Positive	510/285	16.9 (14.2, 19.4)	11.2 (7.9, 14.0)	0.586 (0.463, 0.743)	
Baseline ECOG PS					0.166
1	263/160	13.9 (10.9, 16.3)	7.1 (4.1, 11.6)	0.657 (0.478, 0.904)	
0	400/217	20.6 (15.2, NR)	10.3 (7.5, 11.9)	0.489 (0.373, 0.641)	
Menopausal status					0.246
Pre/Peri-	114/57	NR (17.2, NR)	10.5 (7.4, 15.6)	0.415 (0.246, 0.698)	
Post-	551/321	15.0 (14.1, 17.5)	8.7 (6.5, 11.6)	0.580 (0.463, 0.726)	
Starting dose					0.196
150 mg	491/267	15.3 (14.1, 17.6)	10.5 (7.4, 13.1)	0.602 (0.471, 0.768)	
200 mg	178/112	19.4 (14.4, 24.1)	7.5 (5.7, 11.3)	0.447 (0.305, 0.654)	



Exploratory:

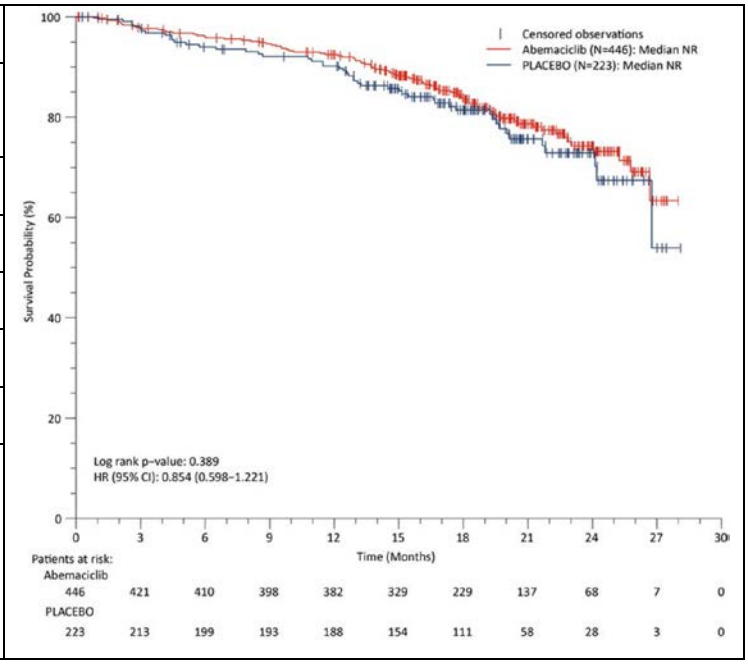
Subgroups Analyzed	n/events	Abemaciclib plus fulvestrant median PFS (95% CI)	Placebo plus fulvestrant median PFS (95% CI)	HR[a] (95% CI)	Interaction p-value[b]
Received prior chemotherapy					0.429
Yes	401/237	14.6 (13.8, 17.5)	10.3 (7.4, 11.6)	0.631 (0.485, 0.821)	
No	139/70	NR (14.7, NR)	11.2 (7.4, 16.9)	0.507 (0.316, 0.814)	
Received prior ET					0.518
Tamoxifen only	182/84	NR (17.6, NR)	13.7 (9.6, 16.8)	0.438 (0.285, 0.673)	
AIs only	280/175	14.1 (11.5, 16.1)	7.4 (5.3, 9.5)	0.590 (0.434, 0.803)	
Both	185/111	14.3 (11.1, 24.0)	9.5 (5.6, 11.6)	0.573 (0.392, 0.837)	
Age group					0.731
<65	424/232	17.4 (15.0, 22.3)	10.8 (7.5, 13.1)	0.523 (0.402, 0.681)	
65 - 74	174/103	14.4 (10.5, 20.6)	8.1 (4.2, 14.7)	0.634 (0.426, 0.942)	
75 - 84	66/41	15.5 (5.1, NR)	5.7 (3.8, 15.2)	0.566 (0.306, 1.046)	
Most recent ET					0.254
AIs	447/277	14.1 (11.8, 16.1)	7.5 (5.7, 10.6)	0.594 (0.465, 0.757)	
Other ET	205/94	NR (18.2, NR)	14.0 (8.9, 16.8)	0.451 (0.301, 0.677)	
Most recent ET					0.045
(Neo)adjuvant	396/224	15.3 (14.1, 19.4)	11.2 (7.5, 14.3)	0.665 (0.508, 0.871)	
Metastatic	256/147	17.6 (14.1, NR)	7.4 (5.6, 11.3)	0.431 (0.311, 0.599)	
Received prior AI					0.213
Yes	465/286	14.1 (12.0, 16.4)	7.5 (5.7, 10.6)	0.585 (0.460, 0.743)	
No	204/93	NR (17.6, NR)	13.7 (9.1, 16.8)	0.433 (0.288, 0.651)	
Prior Lines of ET					0.392
1 line	527/303	15.3 (14.1, 17.2)	9.3 (7.2, 11.6)	0.586 (0.464, 0.739)	
2 lines	125/68	NR (13.9, NR)	10.3 (5.7, 14.3)	0.465 (0.288, 0.749)	



Secondary endpoint – overall survival

The secondary endpoint OS with specified p-value 0.00012 range, was not met:

	ITT	
	Abemaciclib (n=446)	Placebo (=223)
Deaths, n (%)	85 (19)	48 (22)
Censored, n (%)	361 (81)	175 (79)
Alive	353	170
Lost to follow-up	6	4
Patient withdrawal	2	1
Hazard ratio	0.85	
p-value	0.39	



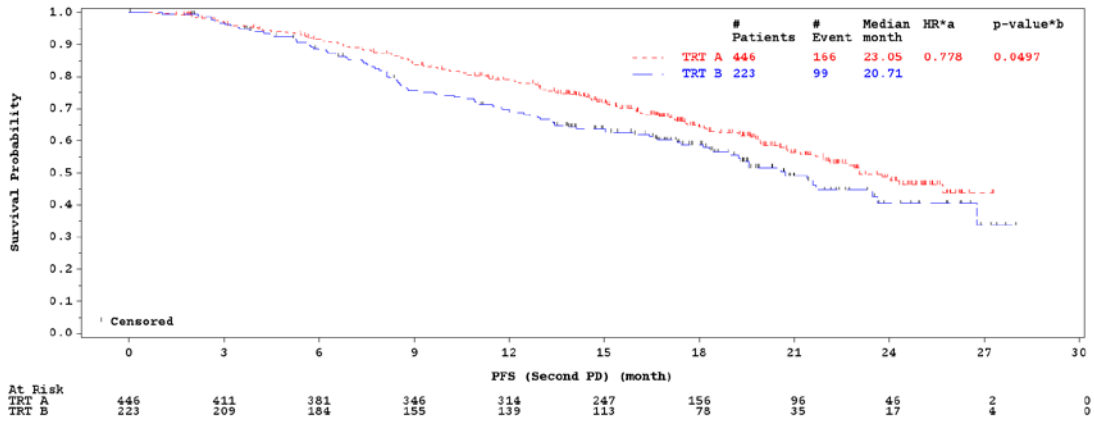
Approximately 20% of population have a death event, similar in both arms. No significant advantage of the combination of abemaciclib plus fulvestrant in OS was seen, although no detrimental effect was suggested either, based on the data provided. The Applicant will provide final OS data post-approval.

Time to Second Disease Progression

The second objective disease progression date was not collected in MONARCH 2 trial. Therefore, the second objective disease progression date was replaced with the discontinuation date of next line (first line of post discontinuation) treatment or starting date of the second line of post-discontinuation treatment, whichever was earlier.

Summary of Time to Second Disease Progression Intent-to-Treat Population MONARCH 2

	Abemaciclib N=446	**Placebo N=223**	**Treatment Effect / Difference / p-Value[c]**
Number of events, n (%)	166 (37.2)	99 (44.4)	
Death without second PD	49 (11.0)	21 (9.4)	
Second PD	117 (26.2)	78 (35.0)	
Number of patients censored, n (%)	280 (62.8)	124 (55.6)	
No baseline tumour assessment	3 (0.7)	0	
No postbaseline tumour assessment	10 (2.2)	4 (1.8)	
No documented PD with regular assessment	202 (45.3)	60 (26.9)	
No documented second PD/death after initial PD	65 (14.6)	60 (26.9)	
Median (95% CI) months	23.1 (21.2, NR)	20.7 (18.3, 23.6)	2.33
p-Value (2-sided) log rank stratified			.0497
Hazard ratio (95% CI) – stratified[b]			0.778 (0.606, 1.000)



Secondary endpoints – best overall response (BOR), overall response rate (ORR), disease control rate (DCR) and clinical benefit rate (CBR)

Best Overall Response[a]	Abemaciclib (N=446) n (%)	Abemaciclib (N=446) 95% CI[b]	Placebo (N=223) n (%)	Placebo (N=223) 95% CI[b]	Difference	Odds Ratio	p-Value[c]
Complete response (CR)	14 (3.1)	1.5, 4.8	1 (0.4)	-0.4, 1.3			
Partial response (PR)	143 (32.1)	27.7, 36.4	35 (15.7)	10.9, 20.5			
Stable disease (SD)	213 (47.8)	43.1, 52.4	133 (59.6)	53.2, 66.1			
≥6 months	165 (37.0)	32.5, 41.5	89 (39.9)	33.5, 46.3			
Progressive disease (PD)	40 (9.0)	6.3, 11.6	45 (20.2)	14.9, 25.4			
Not evaluable[d]	36 (8.1)	5.5, 10.6	9 (4.0)	1.5, 6.6			
Overall response rate (CR + PR)	157 (35.2)	30.8, 39.6	36 (16.1)	11.3, 21.0	19.1	2.82	<.001
Disease control rate (CR + PR + SD)	370 (83.0)	79.5, 86.4	169 (75.8)	70.2, 81.4	7.2	1.56	.025
Clinical benefit rate (CR + PR + SD ≥6 months)	322 (72.2)	68.0, 76.4	125 (56.1)	49.5, 62.6	16.1	2.04	<.001

Abbreviations: CI = confidence interval; CR = complete response; IWRS = interactive web response system; NA = not applicable; N = number of patients in population; n = number of patients; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable

Secondary endpoints for patients with measurable disease[a] – overall response rate (ORR) and clinical benefit rate (CBR)

	Abemaciclib	Placebo
Objective response (measurable disease)	**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.

Secondary endpoints – pain, EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L

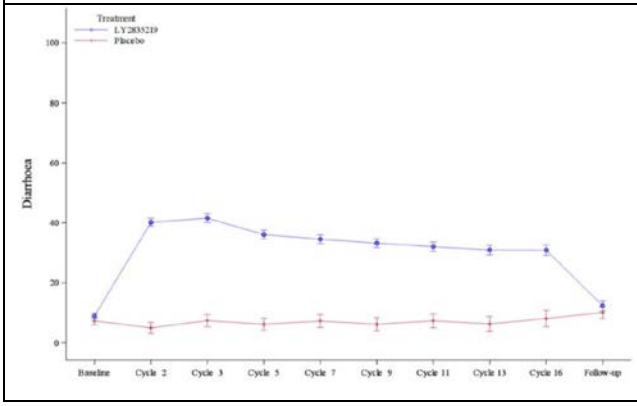
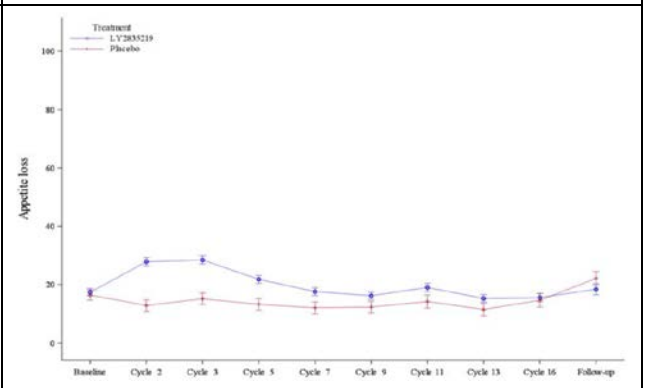
Pain:

The brief pain inventory (BPI) demonstrated a numerical improvement between baseline and post-baseline assessments, but between-group differences of LS mean change from baseline (abemaciclib + fulvestrant versus placebo plus fulvestrant) for mBPI-sf items did not reach clinical or statistical significance.

EORTC QLQ-C30:

	Baseline score		Change from baseline			
	Abemaciclib + fulvestrant	Placebo + fulvestrant	Abemaciclib + fulvestrant	Placebo + fulvestrant	**Difference**	**p-value**
Global health status	64	64	-1.4	0.06	-1.5	.23
Nausea and vomiting	7.0	4.7	4.1	0.65	3.4	<.001
Appetite loss	17	16	3.6	-1.7	5.3	<.001
Diarrhea	8.7	7.4	24	-0.51	25	<.001

Across all post-baseline on-therapy visits, a between-treatment group difference of >20 points was observed in the abemaciclib plus fulvestrant arm, compared to no increase in diarrhea being observed in the placebo plus fulvestrant arm:

EORTC QLQ-C30: diarrhea	**EORTC QLQ-C30: appetite loss**
	

EORTC QLQ-BR23**:**

Similar to MONARCH-3, the *systemic therapy side effect* item was worsened in abemaciclib-treated patients, whereas in contrast to MONARCH-3, the *body image* item was not significantly worse:

	Baseline score		**Change from baseline**			
	Abemaciclib + NSAI	Placebo + NSAI	Abemaciclib + NSAI	Placebo + NSAI	**Difference**	**p-value**
Body image	77	77	-0.97	0.64	-1.6	.25
Systemic therapy side effects	16	16	7.7	2.4	5.2	<.001

EQ-5D-5L:

	Baseline Score Mean (Std Dev)		**Within-treatment Group Change from Baseline[a] LS Mean (SE)**		**Between- treatment Group Change Difference (Abemaciclib – Placebo)[a]**	
	Abemaciclib + Fulv	**Placebo + Fulv**	**Abemaciclib + Fulv**	**Placebo + Fulv**	**LS Mean (SE)[c]**	**p-Value[b]**
Index value	0.72 (0.23)	0.73 (0.22)	0.01 (0.01)	0.00 (0.01)	0.01 (0.01)	.313
Visual analog scale	71.00 (19.48)	71.32 (20.46)	0.12 (0.65)	1.16 (0.92)	-1.05 (1.13)	.354

MONARCH 2: Endocrine-Therapy Naïve Population (Abemaciclib plus Fulvestrant as Initial Endocrine-Based Therapy)

The original MONARCH 2 protocol allowed patients who presented de novo with locally advanced/metastatic disease and not received any prior endocrine therapy (endocrine-naïve, EN).

The Applicant provided the efficacy and safety data from the initially enrolled post-menopausal EN population from the MONARCH 2 study (44 patients), which have been analysed separately and not included in the ITT population, to support the inclusion of the combination of abemaciclib and fulvestrant as initial endocrine-based therapy in the indication.

Numbers analysed: A total of 44 patients were randomized 2:1, 28 in the abemaciclib plus fulvestrant arm and 16 in the placebo plus fulvestrant arm (1 patient in the abemaciclib arm was not treated).

Baseline data: All patients were female, the majority were Caucasian (61.4%), and the median age was 59.5 years (range 36 to 79 years). The majority of patients (61.4%) had a baseline ECOG PS and the majority were postmenopausal (81.8%).

Treatment: 78% patients in the abemaciclib plus fulvestrant arm received abemaciclib at a starting dose of 200 mg Q12H. However, the median dose intensity in the EN population was only slightly higher compared to the EP population (283.4 vs 273.1 mg/day), therefore this is not considered an issue.

Results:

Primary endpoint - PFS by investigator assessment

Table: MONARCH 2 Summary of Progression-Free Survival by Investigator Assessment Endocrine Therapy-Naive Patients Randomized Population

	Abemaciclib N=28	Placebo N=16	Treatment Effect /Difference/p-Value[a]
Number of events, n (%)	9 (32.1)	9 (56.3)	
Death without PD	1 (3.6)	0	
PD	8 (28.6)	9 (56.3)	
Number of patients censored, n (%)	19 (67.9)	7 (43.8)	
No postbaseline tumor assessment	2 (7.1)	0	
No documented PD with regular assessment	17 (60.7)	7 (43.8)	
Median (95% CI) months	NR (19.7, NR)	23.1 (2.01, NR)	
p-Value (2-sided) log rank stratified[b]			p=.0891
Hazard ratio (95% CI) – stratified[b]			0.454 (0.179, 1.154)
PFS survival rate, % (95% CI)[c]			
6 months	84.3 (63.3, 93.8)	68.8 (40.5, 85.6)	15.5 (-11.2,42.3); p=.2554
12 months	80.3 (58.9, 91.3)	62.5 (34.9, 81.1)	17.8 (-10.6, 46.1); p=.2192
18 months	76.0 (54.2, 88.5)	55.6 (28.6, 75.9)	20.5 (-9.4, 50.3); p=.1784

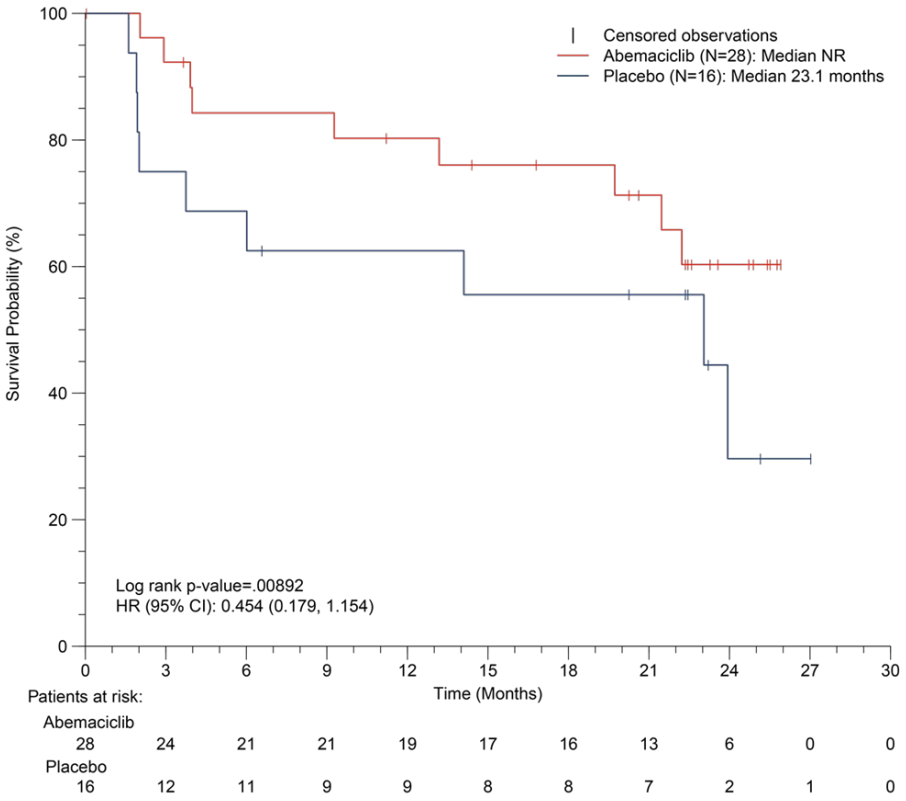
Abbreviations: CI = confidence interval; IWRS = interactive web response system; N = total number of patients in the population within the treatment group; n = number of patients; NR = not reached; PD = progressive disease; PFS = progression-free survival.
Note: PFS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley (1982) and Greenwood (1926).

a Treatment difference/effect/p-values are computed based on comparator placebo.

b Stratified by IWRS nature of disease.

c 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation. Source:o_tte_summ_pfs_2_etnp.rtf.

Figure: MONARCH 2 Kaplan-Meier plot of PFS by investigator assessment, endocrine therapy-naïve patients, randomized population



Abbreviations: HR = hazard ratio; IWRS = interactive web response system; TRT A = abemaciclib plus fulvestrant; TRT B = placebo plus fulvestrant.
*a HR is stratified by IWRS nature of disease.
*b P-value (2-sided) - LOGRANK stratified for IWRS nature of disease comparing with TRT B.
Source: o_tte_figure_kmplot_pfs_etnp.rtf, o_tte_summ_pfs_2_etnp.rtf.

PFS in the EN population by independent review was consistent with the primary analysis by investigator (HR = 0.470, 95%CI 0.148, 1.498).

Secondary endpoints – ORR, DCR, CBR

Table: MONARCH 2 Best Overall Response by Investigator Assessment Endocrine Therapy-Naive Patients Randomized Population

Best Overall Response[a]	Abemaciclib (N=28)		Placebo (N=16)		p-Value[c]
	n (%)	95% CI[b]	n (%)	95% CI[b]	
Complete response (CR)	1 (3.6)	-3.3 – 10.4	0	NA	
Partial response (PR)	11 (39.3)	21.2 – 57.4	8 (50.0)	25.5 – 74.5	
Stable disease (SD)	12 (42.9)	24.5 – 61.2	4 (25.0)	3.8 – 46.2	
≥6 months	8 (28.6)	11.8 – 45.3	3 (18.8)	-0.4 – 37.9	
Progressive disease (PD)	1 (3.6)	-3.3 – 10.4	4 (25.0)	3.8 – 46.2	
Not evaluable[d]	3 (10.7)	-0.7 – 22.2	0	NA	
Overall response rate (CR + PR)	12 (42.9)	24.5 – 61.2	8 (50.0)	25.5 – 74.5	.639

Disease control rate (CR + PR + SD)	24 (85.7)	72.8 – 98.7	12 (75.0)	53.8 – 96.2	.386
Clinical benefit rate (CR + PR + SD ≥6 months)	20 (71.4)	54.7 – 88.2	11 (68.8)	46.0 – 91.5	.850

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; IWRS = interactive web response system; NA = not applicable; N = number of patients in population; n = number of patients; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

a Response criteria used was RECIST version 1.1.

b CIs were based on the normal approximation.

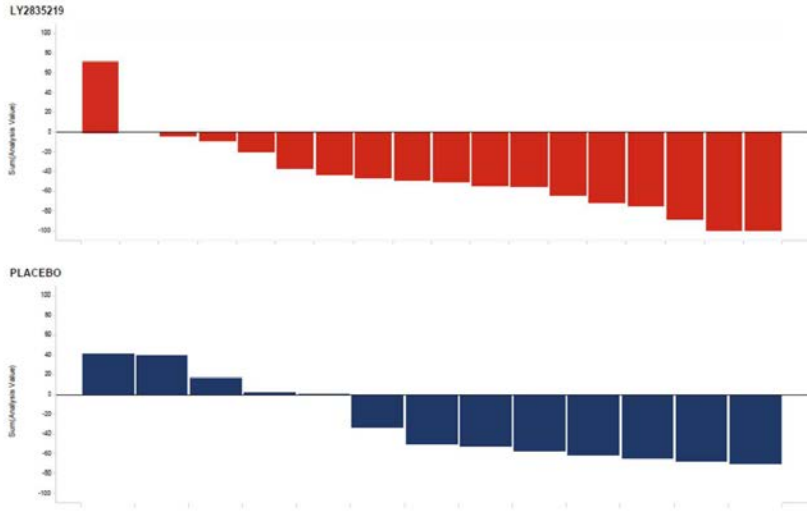
c p-value was calculated by CMH test stratified by the randomization strata IWRS sensitivity to endocrine therapy, IWRS nature of disease. Where a p-value was "NA," the computations were not done because there were fewer than 2 nonmissing levels in the data.

d Patients without adequate tumor assessment prior to treatment discontinuation +30 days or starting new anticancer therapy.

Source: o_rs_best_resp_sum_mult_3_etnp.rtf.

In EN patients with measurable disease, ORR was 60.0% (95% CI: 38.5, 81.5) for the abemaciclib plus fulvestrant arm and 57.1% (95% CI: 31.2, 83.1) for the placebo plus fulvestrant arm (p=.891), as assessed by investigator.

Figure: MONARCH 2 Waterfall plot of best change in tumour size by treatment arm, endocrine therapy-naive patients, randomized population.



Abbreviation: LY2835219 = abemaciclib.

Secondary endpoint – OS

The OS data were immature at the time of data cutoff (5 death events [17.9%] in the abemaciclib plus fulvestrant arm and 4 death events [25%] in the placebo plus fulvestrant arm). The HR was 0.708 (95% CI: 0.186, 2.693), stratified log-rank test p-value = 0.6104. The OS rate at 12 months was 92.3% (95% CI: 72.6, 98.0) in the abemaciclib plus fulvestrant arm and 93.3% (95% CI: 61.3, 99.0) in the placebo plus fulvestrant arm.

As data on second objective disease progression was not collected, discontinuation date of next-line (first line of post-discontinuation treatment), or starting date of the second line of post-discontinuation treatment, whichever was earlier, was investigated as a surrogate:

Summary of Time to Second Disease Progression Endocrine Naïve Population MONARCH 2 by Clinical Study Report Cutoff

	Abemaciclib N=28	Placebo N=16	Treatment Effect /Difference/p-Value[a]
Number of events, n (%)	6 (21.4)	5 (31.3)	
Death without second PD	2 (7.1)	2 (12.5)	
Second PD	4 (14.3)	3 (18.8)	
Number of patients censored, n (%)	22 (78.6)	11 (68.8)	
No postbaseline tumour assessment	2 (7.1)	0	
No documented PD with regular assessment	17 (60.7)	7 (43.0)	
No documented second PD/death after initial PD	3 (10.7)	4 (25.0)	
Median (95% CI) months	NR (22.9, NR)	NR (12.9. NR)	
p-Value (2-sided) log rank stratified[b]			.6893
Hazard ratio (95% CI) – stratified[b]			0.780 (0.231, 2.639)
Second objective PD survival rate, % (95% CI)[c]			
6 months	92.1 (72.1, 98.0)	100.0 (NR, NR)	-7.9 (-18.3, 2.6); .1409
12 months	88.1 (67.6, 96.0)	86.2 (55.0, 96.4)	2.0 (-19.9, 23.8); .8585
18 months	83.7 (62.2, 93.6)	79.0 (47.9, 92,7)	4.8 (-21.0, 30.5); .7172

Abbreviations: CI = confidence interval; IWRS = Interactive Web Response System; N = total number of patients in the population within the treatment group; n = number of patients; NR = not reached; PD = progressive disease; PFS = progression-free survival.

Note: PFS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood.

a Treatment difference/effect/p-values are computed based on comparator placebo.

b Stratified by IWRS nature of disease.

c 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

Figure 4.8. Kaplan-Meier curve of time to second disease progression for endocrine naïve patients.

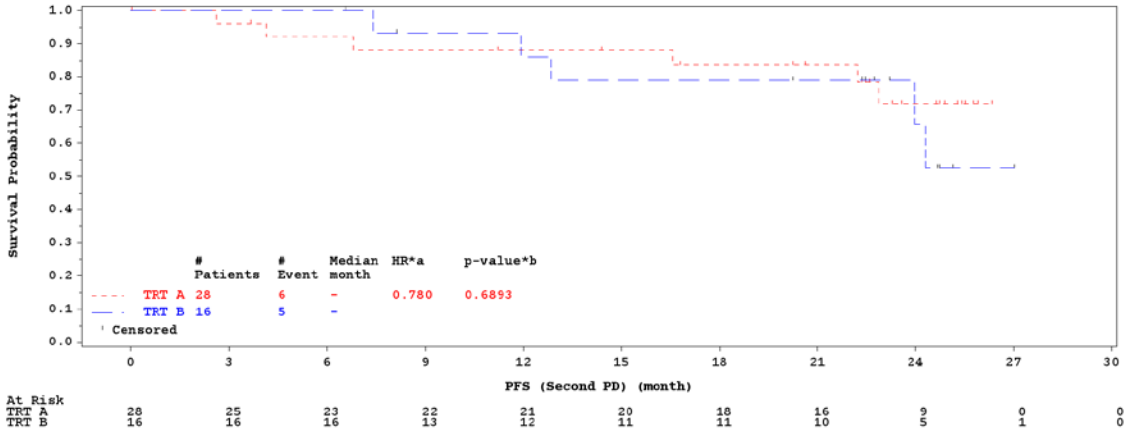


Table 4.2. Summary of Duration of Response for Endocrine Naïve Patients Responder Population – Investigator Assessment MONARCH 2 by Clinical Study Report Cutoff

	Abemaciclib N=12	Placebo N=8
Number of events, n (%)		
PD	2 (16.7)	3 (37.5)
Number of patients censored, n (%)		
No documented PD with regular assessment	10 (83.3)	5 (62.5)
Median (95% CI) months	NR (17.7, NR)	22.0 (1.9, NR)
p-Value (2-sided) log rank unstratified		
Hazard ratio (95% CI) – unstratified		
DoR survival rate, % (95% CI)[a]		
6 months	100 (NR, NR)	87.5 (38.7, 98.1)
12 months	100 (NR, NR)	75.0 (31.5, 93.1)
18 months	88.9 (43.3, 98.4)	75.0 (31.5, 93.1)

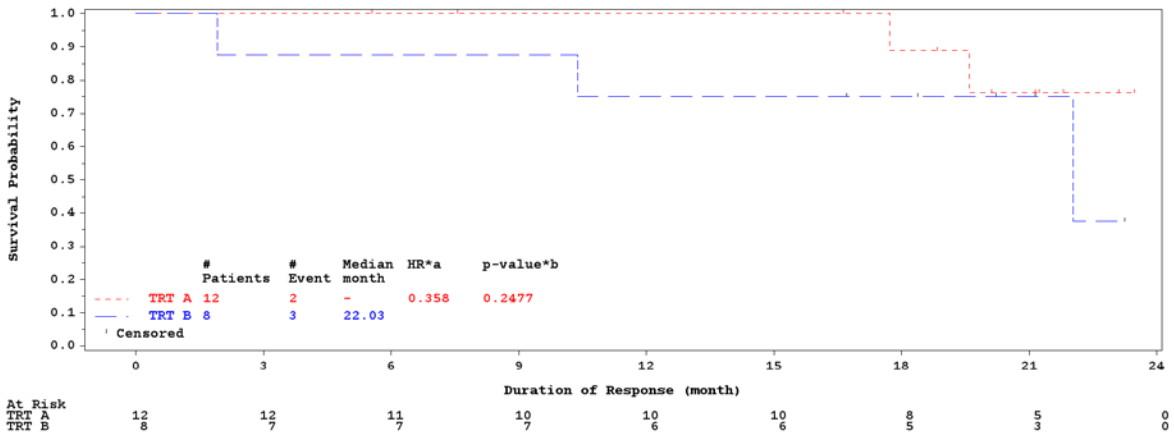
Abbreviations: CI = confidence interval; DoR = duration of response; N = total number of patients in the population within the treatment group; n = number of patients; NR = not reached; PD = progressive disease; PFS = progression-free survival.

Note: PFS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood.

a 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

Source: o_tte_summ_pfs_2_dr_en.rtf.

Figure 4.9. Kaplan-Meier plot of duration of response by investigator assessment for endocrine naïve patients.



Summary of efficacy for trial MONARCH 2

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer	
Study identifier	I3Y-MC-JPBL (MONARCH 2)

Design	Phase 3, randomized (2:1), double blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		study ongoing not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Abemaciclib plus fulvestrant		Abemaciclib 150 mg* orally twice a day, plus plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond. Treatment until PD or other discontinuation criteria were fulfilled. 446 pts randomized.
	Placebo plus fulvestrant		Placebo orally twice a day, plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond. Treatment until PD or other discontinuation criteria were fulfilled. 223 pts randomized.
**NOTE: Protocol Amendment JPBL(a) reduce the starting dose of abemaciclib from 200 mg Q12H to 150 mg Q12H. All patients ongoing at the 200 mg Q12H dose were also required to have their dose reduced to 150 mg Q12H. About 26% of patients were enrolled pre-amendment, and 74% at 150 mg Q12H starting dose post-amendment. Both pre- and post-amendment populations were included in the ITT analysis.*			
Endpoints and definitions	Primary endpoint	PFS	By investigator according to RECIST 1.1. Time from the date of randomization to the date of objective progression or the date of death due to any cause, whichever was earlier.
	(Gated) secondary endpoint	OS	Time from the date of randomization to the date of death from any cause.
	Secondary endpoints	OS at 1, 2, and 3 years; ORR (CR+PR) (per RECIST 1.1 by investigator); duration of response (DoR); disease control rate (DCR =CR+PR+SD); clinical benefit rate (CBR= CR + PR + SD ≥ 6 months); Health Outcome/Quality of Life Measures	
Database lock	Database lock: 14 March 2017		

Results and Analysis

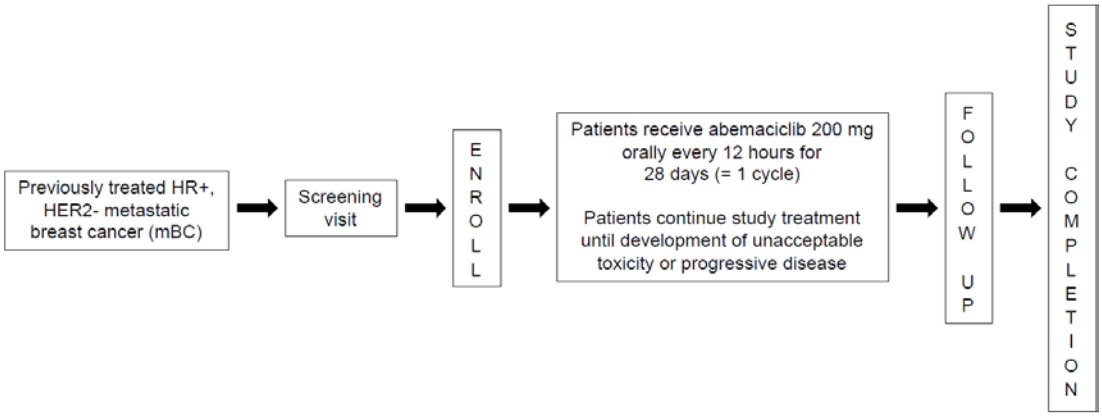
Analysis description	**Primary Analysis (Final)**		
Analysis population and time point description	Intent to treat (669 patients) Data cut-off for the primary PFS analysis: 14 February 2017		
Descriptive statistics and estimate variability; Effect estimate per comparison	Treatment group	Abemaciclib plus fulvestrant	Placebo plus fulvestrant
	Number of subject	446	223
	Primary endpoint		
	PFS N. with events (%)	222 (49.8)	157 (70.4)

	Median PFS months (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 11.4)
	HR (95% CI) p-value (2-sided log rank stratified)	0.553 (0.449, 0.681) p<0.0000001	
	Secondary endpoints		
	OS N. with events (%)	85 (19.1)	48 (21.5)
	Median OS months (95% CI)	NR (26.7, NR)	NR (26.8, NR)
	HR (95% CI) p-value (2-sided log rank stratified)	0.854 (0.598, 1.221) p=0.389	
	ORR (95% CI)	35.2% (30.8, 39.6)	16.1% (11.3, 21.0)
	Odds Ratio p-value	2.82 p<0.001	
	DoR median (months) (95%CI)	NR (18.05, NR)	25.6 (11.9, 25.6)
	DCR (95% CI)	83% (79.5, 86.4)	75.8% (70.2, 81.4)
	Odds Ratio p-value	1.56 p=0.025	
	CBR (95% CI)	72.2% (68.0, 76.4)	56.1% (49.5, 62.6)
	Odds Ratio p-value	2.04 p<.001	

MONARCH 1 (I3Y-MC-JPBN)

A phase 2 study of LY2835219 for patients with previously treated hormone receptor positive, HER2 negative metastatic breast cancer.

Study design



Study participants

Key inclusion criteria

- Female, ≥ 18 years, ECOG ≤ 1.
- Positive for ER and/or PgR by immunohistochemistry (IHC).
- Not positive for HER2 by IHC or in-situ hybridization.
- recurrent, locally advanced, unresectable or metastatic breast cancer with disease progression following anti-estrogen therapy.
- prior treatment with at least 2 chemotherapy regimens:
  - at least 1 of these regimens must have been administered in the metastatic setting.
  - at least 1 of these regimens must have contained a taxane.
  - the additional chemotherapy regimens could have included any of the following: capecitabine, eribulin, gemcitabine, anthracycline, or vinorelbine.
- no more than 2 prior chemotherapy regimens in the metastatic setting.
- Measurable disease according to RECIST 1.1.

Key exclusion criteria

- History or baseline MRI with CNS metastasis.
- Prior CDK4/6 inhibitor, initiated bisphosphonates or RANK-L targeted agent ≤28 days prior to cycle 1 day 1.
- syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest.

Approximately 80% of patients were previously treated with anthracyclines across all settings (12% for metastatic disease).

<u>Objectives and endpoints</u>

- Primary objective: overall response rate (ORR).

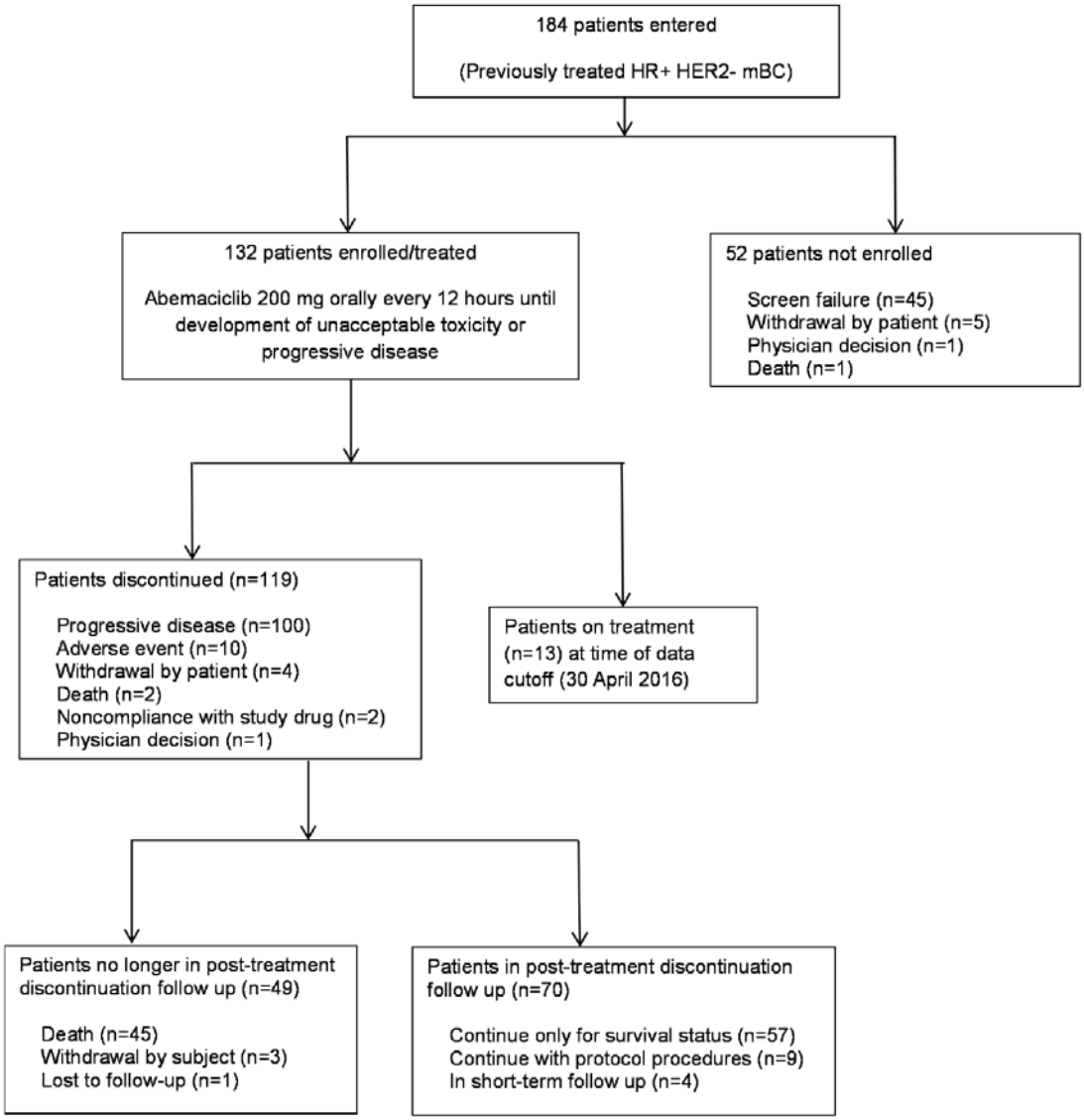
  Confirmation of CR or PR >28 days later was required.
- Secondary objectives: Safety, tolerability, OS, DoR, PFS, disease control rate (DCR), clinical benefit rate (CBR; CR+PR+SD ≥ 6 months), modified Brief Pain Inventory–Short Form (mBPI-sf) and EORTC QLQ-C30.
- PK of abemaciclib and its metabolites.
- Exploratory objectives: biomarkers, Rb pathway, CDK4 and CDK6, cell cycle and the pathogenesis of breast cancer.

The SAP stated that the point estimate and exact p-value for the test of ORR ≤15% versus ORR >15% would be calculated.

An efficacy interim analysis was planned and completed 8 months after the last patient had entered treatment. The 1-sided alpha spent was .000008 for the interim efficacy analysis leaving .024992 for the final efficacy analysis, maintaining an overall 1-sided alpha level of .025.

Recruitment and patient disposition

A total of 184 patients entered the study (signed the ICF) at 35 sites in 4 countries; of these, 52 patients were not enrolled (assigned to study treatment), and 132 patients were enrolled and received at least 1 dose of abemaciclib (USA n= 70, Belgium n= 28, Spain n=23, France n= 11).



The first patient was enrolled 10 June 2014, the last in 30th April 2015, data cutoff was 30 April 2016.

Baseline data

The median age was 58 years (range 36 to 89). All patients were stage IV with a median time since initial diagnosis of 99 months (range 13 to 414 months), and a median time since diagnosis of stage IV disease of 28 months (range 0.1 to 229 months). ECOG performance status was 0 in 55%, 1 in 45%.

The study entry pathological method was histopathology in 89%, cytological in 9.8% and unavailable in 1.5%. Hormone receptor status was ER+/PgR+ in 71%, ER+/PgR- in 27%, ER+/PgR unknown in 1.5% ER-/PgR+ in 0.8%.

Prior lines of endocrine therapy in the metastatic setting had been received by 87%; 36% (1 regimen), 19% (2 regimens), 18% (3 regimens) and 14% (≥ 4 regimens).

Prior lines of chemotherapy in the metastatic setting had been received by 100%; 51% (1 regimen), 49% (2 regimens), 0.8% (3 regimens).

Prior metastatic therapies in more than 10%:

Prior Therapy	Abemaciclib 200 mg N=132 n (%)
Endocrine therapy	
Fulvestrant	67 (50.8)
Exemestane	59 (44.7)
Letrozole	51 (38.6)
Tamoxifen	38 (28.8)
Anastrozole	26 (19.7)
Chemotherapy[a]	
Any taxane	91 (68.9)
Capecitabine	73 (55.3)
Any anthracycline	16 (12.1)
Cyclophosphamide	18 (13.6)
Gemcitabine	10 (7.6)
Vinorelbine	9 (6.8)
Eribulin	6 (4.5)
Ixabepilone	0
Other therapies	
Everolimus	37 (28.0)
Investigational drug	16 (12.1)

Results

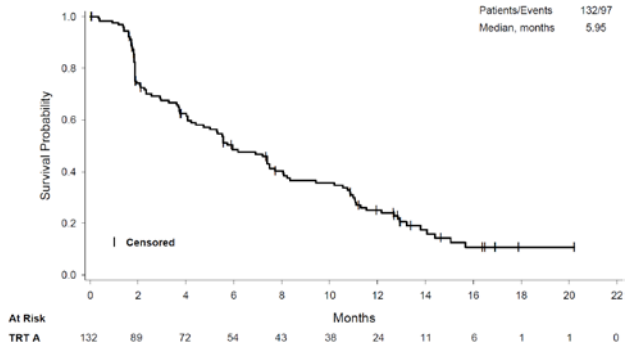
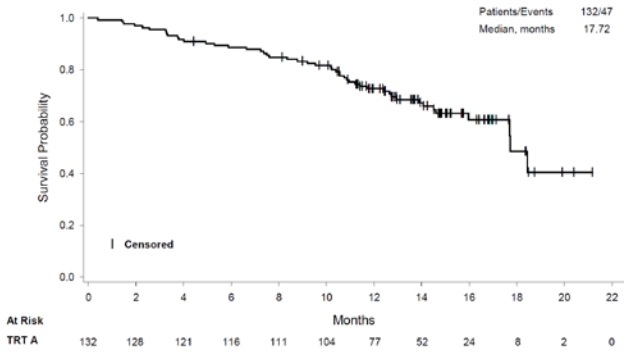
Primary endpoint, best overall response by investigator

The lower bound of the 95% CI did not exclude 15%, which was chosen based on historical data as an ORR representative of what might be expected for approved chemotherapies that might be used in this setting:

	Abemaciclib 200 mg (N=132)			
	n (%)	95% CI[b]	Null Hypothesis Rate (%)	p-Value[c]
Best overall response[a]				
Complete response (CR)	0			
Partial response (PR)	26 (19.7)			
Stable disease (SD)	63 (47.7)			
<6 months	33 (25.0)			
≥6 months	30 (22.7)			
Progressive disease	34 (25.8)			
Not evaluable/not assessed[d]	9 (6.8)			
Objective response rate (CR + PR)	26 (19.7)	(13.3, 27.5)	15.0	0.1715
Disease control rate (CR + PR + SD)	89 (67.4)	(58.7, 75.3)		
Clinical benefit rate (CR + PR + SD ≥6 months)	56 (42.4)	(33.9, 51.3)		

Secondary objectives: OS, DoR, PFS, modified Brief Pain Inventory–Short Form (mBPI-sf) and EORTC QLQ-C30.

In the investigator assessment, the median time to response was 3.7 months (range: 1.1 to 14 months). Of the 26 patients in MONARCH 1 with a PR as assessed by the investigator, 16 progression events and 1 death were observed. The median DoR was 8.6 months (95% CI: 5.8, 10).

PFS by investigator	**OS**
	

In support of PFS, the applicant analysed time-to-progression on last prior chemotherapy. This was derived for 130 patients using the progression date recorded in the case report form (CRF), or the end date of the treatment when not reported (in 10 patients). The median TTP on the last prior chemotherapy was 6.6 months with an interquartile range of 3.5 to 11.1 months. Further analyses were performed, indicating that the PFS (but not ORR) was similar in patients with long or short TTP on last prior chemotherapy. Although the comparison to last prior therapy is considered interesting, and potentially providing an internal control for the PFS result, findings are not reassuring and do not outweigh the modest response rate and uncertainties identified.

Secondary objectives: modified Brief Pain Inventory–Short Form (mBPI-sf) and EORTC QLQ-C30.

The applicant has made no overall interpretation of the mBPI-sf of EORTC QLQ-C30 findings.

Comparison to the Flatiron Health database.

In order to place the MONARCH 1 OS data in clinical context, OS results from a retrospective cohort study using observational data from the Flatiron Health EMR database for patients with mBC are presented. The Flatiron Metastatic Breast Cancer Cohort includes more than 15,000 patients (as of 28 February 2018) with mBC. It is part of a broader longitudinal database containing electronic health record data from over 265 cancer clinics representing approximately 800 sites of care across the US.

The Flatiron cohort includes patients with a mBC diagnosis from 01 January 2011 to 28 February 2018. To provide the most relevant comparator to MONARCH 1 patient population, the following entry criteria are used:

- mBC patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

- received monotherapy with capecitabine, gemcitabine, eribulin, or vinorelbine. These agents were selected based on ESMO and NCCN guidelines for sequential single-agent chemotherapy for patients in this setting
- received at least 1 but no more than 2 lines of chemotherapy in the metastatic setting prior to receipt of the single-agent chemotherapies listed above. Patients who received CDK4 and CDK6 drugs (for example, palbociclib, ribociclib, and abemaciclib) in prior lines of therapy will be excluded.

Patients were further matched on age group, race group, number of prior chemotherapies in the metastatic setting, number of prior endocrine therapies in the metastatic setting, prior capecitabine use, and progesterone receptor status, utilizing the Mahalanobis distance matching method (Rubin 1980).

Table 4.1. Group Comparison Prior to and after Mahalanobis Distance Matching

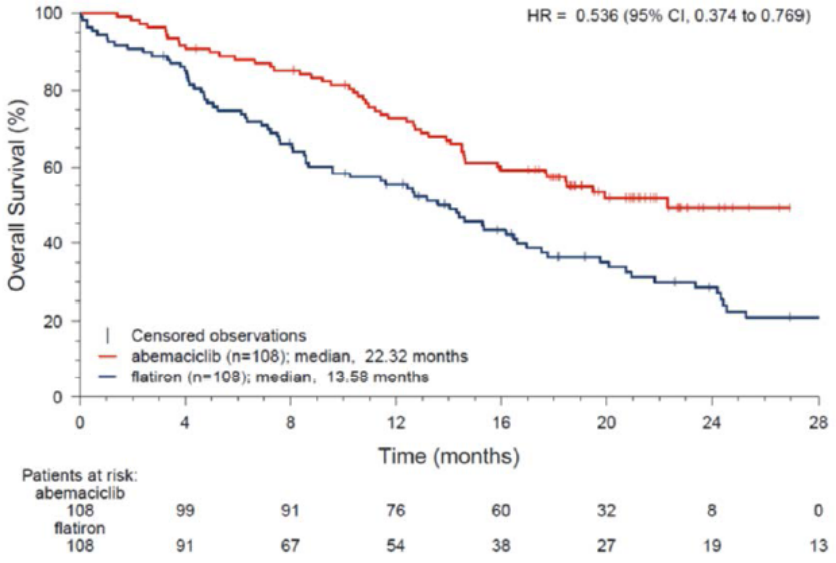
	Before Matching			After Matching		
Factors	MONARCH 1 N=132	Flatiron N=281	p-Value	MONARCH 1 N=108	Flatiron N=108	p-Value
Pooled age group, n (%)			0.0308			1.000
<65 years old	90 (68.2)	159 (56.6)		72 (66.7)	71 (65.7)	
≥65 years old	42 (31.8)	122 (43.4)		36 (33.3)	37 (34.3)	
Pooled race group			<0.0001			0.5689
Caucasian	124 (93.9)	192 (68.3)		100 (92.6)	103 (95.4)	
Other	8 (6.1)	89 (31.7)		8 (7.4)	5 (4.6)	
Number of prior chemotherapies in the metastatic setting			0.2899			0.7829
1 Regimen	67 (50.8)	159 (56.6)		61 (56.5)	64 (59.3)	
2 Regimens	65 (49.2)	122 (43.4)		47 (43.5)	44 (40.7)	
Number of prior ET in the metastatic setting			<0.0001			0.9840
None	17 (12.9)	114 (40.6)		17 (15.7)	16 (14.8)	
1 Regimen	48 (36.4)	77 (27.4)		40 (37.0)	42 (38.9)	
2 Regimens	25 (18.9)	54 (19.2)		23 (21.3)	24 (22.2)	
≥ 3 Regimens	42 (31.8)	36 (12.8)		28 (25.9)	26 (24.1)	
Prior capecitabine use			<0.0001			0.5859
Yes	76 (57.6)	73 (26.0)		54 (50.0)	59 (54.6)	
No	56 (42.4)	208 (74.0)		54 (50.0)	49 (45.4)	
Progesterone receptor status			0.0902			0.8794
Negative	35 (26.5)	99 (35.2)		29 (26.9)	31 (28.7)	
Positive	95 (72.0)	179 (63.7)		79 (73.1)	77 (71.3)	

Abbreviation: N = number of patients.
Note: Fisher's exact test is used for p-value.
Patients with missing baseline demographics or disease characteristics were removed from the analysis.
Source: maha_match_sptdc_in1.rtf.

Table 4.2. Summary of Matched Adjusted Overall Survival MONARCH 1 versus Flatiron Retrospective Study Cohort

	MONARCH 1 N=108	Flatiron N=108
Number of deaths, n (%)	50 (46.3)	79 (73.1)
Number of patients censored, n (%)	58 (53.7)	29 (26.9)
Median (95% CI) months	22.3 (16.0, NR)	13.6 (9.6, 16.6)
Survival rate, % (95% CI)		
4 months	91.7 (84.6, 95.6)	85.1 (76.9, 90.6)
8 months	85.1 (76.9, 90.6)	66.1 (56.2, 74.2)
12 months	72.7 (63.2, 80.2)	55.2 (45.1, 64.1)
16 months	59.2 (49.2, 67.9)	43.3 (33.5, 52.8)
20 months	51.6 (41.1, 61.1)	35.0 (25.6, 44.6)
24 months	49.1 (38.1, 59.2)	28.5 (19.5, 38.1)
Hazard ratio (95% CI)[a]	0.536 (0.374, 0.769)	

Abbreviations: CI = confidence interval; N = total number of patients in matched adjusted group; n = number of patients; NR = not reached; OS = overall survival.
Note: OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood.
[a] Flatiron is used as the comparator.
Source: o_tte_summ_os_rwe_in_maha1.rtf.



Source: km_os_maha1.pdf.

Figure 4.1. **Kaplan-Meier plot matched adjusted overall survival MONARCH 1 versus Flatiron patients.**

It is entirely unclear whether this is representative of the difference in OS that would be seen in a randomized comparative trial. In the current disease setting, with an ORR of 20%, the numerical OS difference compared to external data is considered a critically uncertain evidence of clinical benefit.

The Applicant proposed to initiate a Phase 3 study of abemaciclib versus physician's choice single-agent chemotherapy as a post-authorisation measure for the monotherapy indication. However, the feasibility of the proposed study is questioned after the approval of abemaciclib monotherapy.

Summary of efficacy for trial MONARCH 1

Title: A Phase 2 Study of LY2835219 for Patients with Previously Treated Hormone Receptor Positive, HER2 Negative Metastatic Breast Cancer			
Study identifier	I3Y-MC-JPBN (MONARCH 1)		
Design	Phase 2, open label, single arm, multicenter trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		completed (18 months after the enrollment of the last patient) not applicable not applicable
Hypothesis	Exploratory (single arm) H0 response rate of abemaciclib was ≤15% vs Ha response rate was >15% using a binomial exact test. Power 82% at an overall 1-sided alpha level of 0.025 assuming a true response rate of 25%.		
Treatment group *(single arm)*	Abemaciclib		200 mg Q12H Patients were treated until there was evidence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met. 132 patients treated
Endpoints and definitions	Primary endpoint	ORR	(CR+PR) evaluated by investigator according to RECIST 1.1 Responses must have been confirmed
	Secondary endpoint	DoR	from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever was earlier
	Secondary endpoint	PFS	from the date of first dose of abemaciclib to the date of objective progression or the date of death due to any cause, whichever was earlier
	Secondary endpoint	OS	from the date of first dose of abemaciclib to the date of death from any cause.
	Secondary endpoint	DCR	CR + PR + SD
	Secondary endpoint	CBR	CR + PR + SD ≥ 6 months
	Secondary endpoints: safety, Impact on pain, disease symptoms and QoL		
Database lock	10 May 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All enrolled population (all patients who received at least 1 dose of study treatment) Cut-off date 30 April 2016		
Descriptive statistics and estimate variability	Treatment group *(single arm)*		Abemaciclib
	Number of subjects		132

	ORR by investigator (95%CI)	0 CR + 26 PR **19.7% *** (13.3, 27.5)
	ORR by independent review (95%CI)	0 CR + 23 PR 17.4% (11.4, 25.0)
	DoR median (95%CI)	8.6 months (5.8, 10.2)
	TTR median (95%CI)	3.7 months (1.1 - 14.2)
	DCR (95% CI)	67.4% (58.7, 75.3)
	CBR (95% CI)	(42.4), (33.9, 51.3)
	PFS by investigator median (95% CI)	6 months (4.2, 7.5)
	PFS by independent review median(95% CI)	5.9 months (3.7, 8.1)
	OS median (95% CI)	22.3 months (17.7, NR)
Notes	* Null Hypothesis Rate for ORR: 15%, p-value 0.1715	

2.9.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The overall design of the randomized, active-controlled studies MONARCH-3 and MONARCH-2 was acceptable.

Patient populations in the randomized trials, as identified by eligibility criteria, were relevant to the respective 1st advanced line indication of abemacilib as add on to a non-steroidal AI, and the 2nd line indication as add-on to fulvestrant. The chosen comparators were appropriate, in keeping with international guidelines.

In advanced breast cancer, prolonging survival and alleviating disease symptoms are relevant aims of therapy. Cure is not expected. Although OS is the most persuasive endpoint, PFS is an acceptable primary endpoint.

Foreseeable benefits of the PFS gain include delayed symptomatic deterioration, postponed chemotherapy, and extension of life span provided no disease-modifying effects of abemaciclib beyond discontinuation. Such an effect has been discussed for CDK 4/6 inhibitors; some practitioners have reported fast disease progression upon drug withdrawal. Therefore, in the absence of mature OS data, PFS 2, TFST and TSST are considered important supporting evidence. In relation to scientific advice sought (EMA/CHMP/SAWP/140264/2014), the CHMP highly recommended analysis of PFS2. During the procedure, the applicant submitted analyses of time to the earlier of next line discontinuation/start of 2nd next line treatment, which in view of findings was considered an acceptable surrogate provided subsequent submission of final OS data. The Applicant is recommended to submit interim and final OS data.

Both Study I3Y-MC-JPBM (Monarch 3) and Study I3Y-MC-JPBL (Monarch 2) were double-blind. Considering e.g. the frequently reported occurrence of diarrhoea, performing blinded independent central review (BICR) of scans rather than on a subset (as initially planned) is endorsed.

Both Study I3Y-MC-JPBM and Study I3Y-MC-JPBL had a 2-look group-sequential design of the primary endpoint of investigator-assessed PFS. The approach to handle multiplicity taking into account repeated analyses over time and the importance of the key secondary endpoint of OS seems appropriate.

Study I3Y-MC-JPBM (Monarch 3), was planned to enrol approximately 450 patients, 300 patients in the abemaciclib plus NSAI arm and 150 patients in the placebo plus NSAI arm. Initially, the sample size estimation was based on a hazard ratio of 0.714. Per protocol amendment (a), the number of events required was decreased from 312 to 270 and the assumed hazard ratio was changed to 0.67. With protocol amendment (b), the number of events was further decreased (from 270 to 240) based on recent Phase 3 study disclosures (Finn et al. 2016; Hortobagyi et al. 2016; PALOMA 2 and MONALEESA 2) indicating that the combination of a non-steroidal aromatase inhibitor and an inhibitor of CDK4 and CKD6 may be highly efficacious. This is endorsed considering both the fairly limited original sample size, the 2:1 randomisation and that the changes made were justified by the belief in a larger difference between treatments than initially assumed.

Study I3Y-MC-JPBL (Monarch 2) was to enrol approximately 550 patients in two strata of patients according to prior endocrine therapy: endocrine therapy pretreated (EP) patients and endocrine therapy naïve (EN) patients. Per amendment (a) the starting dose of blinded study drug was changed from 200 mg Q12H to 150 mg Q12H. Following this dose change the study was modified to focus the study objectives on the EP strata; the inclusion of endocrine therapy naïve (EN) patients was removed and enrolment to the study was to continue until 450 EP patients had been enrolled at a starting dose of 150 mg Q12H. This was the approximate target number of EP patients at the planning stage of the study. The revised definition of the ITT population excluded only those patients previously randomised within a specific randomisation stratum. As a result, the treatment balance was preserved within the revised ITT population and remained balanced also with respect to the other stratification factor (nature of disease).

For both studies, the statistical analysis plan was overall acceptable. Generally, commonly expected methods were used. Pre-specified PFS censoring rules implied censoring “only” if baseline or post-baseline data was missing, a patient was lost to follow-up or in case of no event. Data from a patient was also to be censored if documented progression or death occurred after two or more missed consecutive post-baseline tumour assessments. This approach may suggest the planning of a sensitivity analysis taking all events into account irrespective of when they occurred. No such analysis was planned nor has been performed (irrespective of study; this concerned only a few patients). Several (other) sensitivity analyses using different censoring rules were however planned and performed (same in both studies).

In both studies, a number of changes to the analyses were implemented. These changes were stated to have been based on external data, thus no concern is raised. They further derived from updates to the OS analysis plan. In Study I3Y-MC-JPBM, specifically, the pooled (JPBL and JPBM) overall survival analysis was reclassified as an exploratory analysis and a visceral disease (VIS) population was defined with the gated analysis of OS updated to split alpha between the ITT population and the population of patients with visceral disease at baseline.

The design of the single-arm study I3Y-MC-JPBN is overall acceptable as an exploratory study. In scientific advice, it was discussed as pivotal in the context of conditional approval (EMA/CHMP/SAWP/140264/2014).

Efficacy data and additional analyses

In MONARCH-3 (I3Y-MC-JPBM), the pre-planned interim analysis was performed with a data cut-off point being approximately 189 investigator-assessed PFS events (31 Jan 2017). The final analysis was conducted when 246 investigator-assessed PFS events had been observed (3 Nov 2017).

At interim, the median was not reached (NR) vs. 15 months in abmaciclib + NSAI vs. placebo + NSAI, HR 0.54 (p = 0.000021) for PFS by investigator, with an event rate of 32% and 52% for the experimental and control arms, respectively. The PFS finding was supported by independent review and in sensitivity analyses, and further by an ORR of 48% vs. 35%, OR 1.8 (nominal p= 0.002) in favor of abemaciclib. The final analysis was consistent, with 28 vs. 15 months duration, HR 0.54 (p = 0.000002) for PFS by investigator, with an event rate of 42% and 66%.

The time to the earlier of next line discontinuation/start of 2nd next line treatment (PFS 2 surrogate) was 31 vs. 28 months in abmaciclib + NSAI vs. placebo + NSAI, HR 0.74 (p = 0.043), with an event rate of 33% and 45% for the experimental and control arms, respectively. The median difference of 2.7 months was poorly representative for the overall effect (~10 months may be a better representation given the HR of 0.74).

For OS, the median was NR vs. NR, HR 0.97 (p= 0.92), with an event rate 9.8% vs. 10% at interim PFS, and NR vs. NR, HR 1.1 (p= 0.80), with an event rate 19% vs. 18% at final PFS analysis.

Based on the data provided on patient reported outcomes, it is noted that the addition of abemaciclib to hormonal treatment is affecting patients mostly due to diarrhoea. However, global health status was similar at baseline in both arms and no significant difference was evident throughout the treatment.

In MONARCH-2 (I3Y-MC-JPBL), the criteria for a positive study were not met at the PFS interim analysis and the final analysis of PFS was performed (submitted within this application). The sponsor remained blinded to the interim results and was not unblinded until the primary analysis of PFS. No changes to the analyses were made between the interim and the final analysis of PFS.

The median PFS was 16 vs. 9.3 months in abmaciclib + fulvestrant vs. placebo + fulvestrant patients, HR 0.55 (p = 0.0000001), with an event rate of 50% vs. 70%. The PFS gain is clinically relevant, and the PFS finding was supported by independent review and in sensitivity analyses, and further by an ORR of 35% vs. 16%, OR 2.8 (nominal p< 0.001) in favor of abemaciclib.

The time to the earlier of next line discontinuation/start of 2nd next line treatment (PFS 2 surrogate) was 23 vs. 21 months in abmaciclib + fulvestrant vs. placebo + fulvestrant, HR 0.78 (p = 0.050, with an event rate of 37% and 44% for the experimental and control arms, respectively.

For OS, the medians were NR vs. NR, HR 0.85 (p= 0.39), with an event rate 19% vs. 22%.

Thus, overall survival data is immature with about 20% event rate in MONARCH 2 and 3. The post progression disease-course is probed in the time to the earlier of next line discontinuation/start of 2nd next line treatment analyses, and indicate a preserved positive effect. Final OS data is recommended to be submitted for confirmation.

Global health status evaluated by EORTC QLQ-C30 questionnaire appeared similar between arms and stable throughout the treatment. The higher difference in global health status is seen at cycle 2 in favour of abemaciclib (possibly due to early diarrhoea), then the curves are overlapping.

In MONARCH-1, the ORR was 20% (CI: 13.3 – 27.5), the CBR (≥ 6 months) 42%, PFS 6.0 months, and OS 22 months.

In planning MONARCH-1, an ORR of 15% had been identified as surpassing that of any agent used in this patient population; this lower bound was not met (ORR 20%, CI 13% - 28%). In scientific advice (EMA/CHMP/SAWP/140264/2014), the CHMP did not object to this boundary, but it was made clear that considering one single-arm phase 2 study to support approval (conditional was discussed), hurdles could be foreseen as results would have to be compelling and obvious to any qualified observer.

External data forwarded by the MAH for contextualization was limited and heterogeneous, and offered an uncertain reference for the MONARCH-1 findings. Also, as notable add-on effects have been demonstrated with CDK 4/6 inhibitors also after progression on endocrine therapy, the proposed monotherapy indication appeared pharmacologically and clinically unjustified. A positive B/R could not be concluded for the proposed monotherapy indication.

The extrapolation to AI + LHRH in premenopausal women can be accepted. Efficacy has been shown for abemaciclib in combination with AI in postmenopausal patients, and in combination with fulvestrant + LHRH in pre/perimenopausal patients, supporting the extrapolation. Furthermore, AI + LHRH constitutes an accepted alternative (to antioestrogens/SERMs) in premenopausal patients, including as first line therapy, according to current clinical practice and European and international therapy guidelines. Effective inhibition of ER signalling is achieved with AI or fulvestrant (+LHRH) alike, as this is the basis for anti-tumour activity of these compounds. This further supports that abemaciclib can be used as add-on, not only to fulvestrant +LHRH, but also to AI +LHRH. Efficacy of abemaciclib + fulvestrant in the endocrine-naïve population may be supported from use with fulvestrant in the second-line setting, and from combination with AI in first line.

2.9.4. Conclusions on the clinical efficacy

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

The ORR seen in the single arm MONARCH-1 trial undertaken in a chemotherapy-experienced metastatic breast cancer population is not outstanding and clinical benefit has not been shown. The Applicant revised the indication to remove the monotherapy.

2.10. Clinical safety

The safety database encompasses patients treated with abemaciclib in combination with AI in the MONARCH 3 study (N=327), in combination with fulvestrant in the MONARCH 2 study (N=441) and as monotherapy in the MONARCH 1 study (N=132). Overall, approximately 900 patients have received abemaciclib in combination with endocrine therapy and 732 patients and healthy subjects received single-agent abemaciclib in 17 clinical trials.

This safety assessment has focused on the three studies i.e. MONARCH 3, MONARCH 2 and MONARCH 1.

MONARCH 3 (I3Y-MC-JPBM, abemaciclib plus AI)

A 2:1 randomized, double-blind Phase III study evaluating abemaciclib with NSAI or placebo with NSAI as 1st line treatment in postmenopausal women with HR+, HER2- locally advanced or metastatic breast cancer.

Data cut-off date 03 November 2017

The safety population included 488 randomized (327 patients in the abemaciclib + AI arm and 161 patients in the control arm). The investigator determined the specific AI (letrozole or anastrozole) to be administered to the patients. Approximately 80% of patients received letrozole and 20% received anastrozole.

Patient exposure

No difference is observed in terms of median number of cycles of abemaciclib received per patient (16 cycles) compared to the median number of cycles in the control arm (15 cycles). The duration of exposure is likely affected by the duration of follow-up up to the data cut-off date for this primary analysis (median ~18 months in both arms). In regard to dose intensity, the median and the mean for the experimental arm was 256 mg/day and 238 mg/day respectively compared to the control (295 mg/day and 285 mg/day). A difference in terms of relative dose intensity was also observed with a median of 85 % and a mean of 79 % for the experimental arm as compared to median 98 % and mean 95 % in the control arm thus indicating a lower tolerability for the investigational combination.

Dose Adjustments and Omissions

A total of 47 % and 7 % had dose reductions in the experimental arm and control arm respectively. About 25 % of the patients needed only one dose reduction whilst 21 % had two and few required three dose reductions. The majority was attributed to AEs (47 % in the experimental arm and 6 % in the control arm). AEs leading to abemaciclib dose reductions included mainly diarrhoea (14 %) and neutropenia (13 %).

A total of 65 % had at least one abemaciclib dose omission with 60 % due to AEs. Of note, about 27 % needed ≥ 3 dose omissions. The main overall cause was neutropenia (17 %) and diarrhoea (15 %).

Adverse events

ADR definition

The criteria used in the assessment of MONARCH 3 safety data were as follows:

1. p-value <.05 and odds ratio (OR)>1 (missing ORs are considered >1). An OR >1 indicates a higher incidence in the abemaciclib arm.

2. OR ≥ 2 and abemaciclib incidence ≥ 1% before rounding and abemaciclib count ≥4 (missing ORs are considered >2).

3. Abemaciclib incidence ≥10% before rounding and OR>1 (missing ORs are considered >1).

Overview of AEs, Safety Population, MONARCH 3

	Number (%) of Patients	
Number of Patients[a]	Abemaciclib + NSAI N=327	Placebo + NSAI N=161
Patients with ≥1 TEAE	323 (98.8)	152 (94.4)
Related to study treatment[b]	309 (94.5)	91 (56.5)
Patients with ≥1 CTCAE ≥Grade 3 TEAE	202 (61.8)	42 (26.1)
Related to study treatment[b]	168 (51.4)	11 (6.8)
Patients with ≥1 SAE	102 (31.2)	27 (16.8)
Related to study treatment[b]	41 (12.5)	4 (2.5)
Patients who discontinued study treatment due to an AE[c]	54 (16.5)	5 (3.1)
Related to study treatment[b]	39 (11.9)	0
Patients who discontinued study treatment due to an SAE[c]	21 (6.4)	5 (3.1)
Related to study treatment[b]	12 (3.7)	0
Patients who died due to an AE on study treatment[d]	8 (2.4)	2 (1.2)
Related to study treatment[b]	4 (1.2)	0
Patients who died due to an AE within 30 days of discontinuation from study treatment[d]	3 (0.9)	0
Related to study treatment[b]	1 (0.3)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; NSAI = nonsteroidal aromatase inhibitor; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Patients may be counted in >1 category.

b Includes events that were considered related to study treatment as judged by the investigator.

c Patients who died on study treatment with primary cause as AE or SAE were also included as discontinuations.

d Deaths were also included as SAEs and discontinuations due to AEs.

Source: o_ae_overview_2_old.rtf.

For contextualization, duration on therapy was similar between the experimental and control arm (16 and 15 months respectively). A quite substantial difference in the proportion of patients experiencing Grade ≥3 AEs and SAE is observed in the experimental arm compared to the control arm (62 % versus 26 % and 31 % versus 17 % in the respective arms) with the majority considered treatment related. On the other hand, this appears not to translate into treatment discontinuations of the same magnitude, which may point to a manageable safety profile with appropriate risk minimization measures. A discontinuation rate attributed to AEs of 17 % is considered acceptable.

TEAEs by Maximum CTCAE Grade Experienced by ≥ 10% of Population in Either Arm Preferred Term by Decreasing Frequency (All Grades) in the abemaciclib Plus NSAI Arm

	Abemaciclib + NSAI N=327					Placebo + NSAI N=161				
	CTCAE Grade									
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Patients with ≥1 TEAE, n (%)	19 (5.8)	102 (31.2)	169 (51.7)	22 (6.7)	323 (98.8)	40 (24.8)	70 (43.5)	36 (22.4)	4 (2.5)	152 (94.4)
Diarrhea	139 (42.5)	99 (30.3)	31 (9.5)	0	269 (82.3)	36 (22.4)	14 (8.7)	2 (1.2)	0	52 (32.3)
Neutropenia	12 (3.7)	53 (16.2)	72 (22.0)	6 (1.8)	143 (43.7)	0	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.9)
Fatigue	70 (21.4)	59 (18.0)	6 (1.8)	NA	135 (41.3)	33 (20.5)	21 (13.0)	0	NA	54 (33.5)
Nausea	91 (27.8)	40 (12.2)	4 (1.2)	NA	135 (41.3)	30 (18.6)	1 (0.6)	2 (1.2)	NA	33 (20.5)
Anemia	31 (9.5)	49 (15.0)	23 (7.0)	0	103 (31.5)	8 (5.0)	3 (1.9)	2 (1.2)	0	13 (8.1)
Abdominal pain	72 (22.0)	24 (7.3)	6 (1.8)	NA	102 (31.2)	13 (8.1)	6 (3.7)	2 (1.2)	NA	21 (13.0)
Vomiting	66 (20.2)	28 (8.6)	5 (1.5)	0	99 (30.3)	15 (9.3)	2 (1.92)	4 (2.5)	0	21 (13.0)
Alopecia	83 (25.4)	7 (2.1)	NA	NA	90 (27.5)	18 (11.2)	0	NA	NA	18 (11.2)
Decreased appetite	51 (15.6)	30 (9.2)	5 (1.5)	0	86 (26.3)	13 (8.1)	3 (1.9)	1 (0.6)	0	17 (10.6)
Leukopenia	13 (4.0)	31 (9.5)	27 (8.3)	1 (0.3)	72 (22.0)	2 (1.2)	1 (0.6)	0	1 (0.6)	4 (2.5)
Blood creatinine increased	35 (10.7)	25 (7.6)	6 (1.8)	1 (0.3)	67 (20.5)	6 (3.7)	1 (0.6)	0	0	7 (4.3)
Headache	51 (15.6)	11 (3.4)	3 (0.9)	NA	65 (19.9)	20 (12.4)	6 (3.7)	0	NA	26 (16.1)
ALT increased	20 (6.1)	16 (4.9)	20 (6.1)	1 (0.3)	57 (17.4)	6 (3.7)	3 (1.9)	3 (1.9)	0	12 (7.5)
Arthralgia	43 (13.1)	14 (4.3)	0	NA	57 (17.4)	26 (16.1)	7 (4.3)	0	NA	33 (20.5)
Constipation	43 (13.1)	12 (3.7)	2 (0.6)	0	57 (17.4)	18 (11.2)	5 (3.1)	0	0	23 (14.3)
AST increased	28 (8.6)	15 (4.6)	12 (3.7)	0	55 (16.8)	8 (5.0)	2 (1.2)	2 (1.2)	0	12 (7.5)
Back pain	31 (9.5)	18 (5.5)	3 (0.9)	NA	52 (15.9)	15 (9.3)	10 (6.2)	1 (0.6)	NA	26 (16.1)
Rash	36 (11.0)	11 (3.4)	3 (0.9)	0	50 (15.3)	6 (3.7)	2 (1.2)	0	0	8 (5.0)
Cough	36 (11.0)	12 (3.7)	0	NA	48 (14.7)	16 (9.9)	4 (2.5)	0	NA	20 (12.4)
Pruritus	37 (11.3)	10 (301)	0	NA	47 (14.4)	14 (8.7)	1 (0.6)	0	NA	15 (9.3)
Dizziness	35 (10.7)	8 (2.4)	1 (0.3)	NA	44 (13.5)	15 (9.3)	3 (1.9)	0	NA	18 (11.2)
Stomatitis	34 (10.4)	7 (2.1)	0	0	41 (12.5)	12 (7.5)	5 (3.1)	0	0	17 (10.6)

Continued

	Abemaciclib + NSAI N=327					Placebo + NSAI N=161				
	CTCAE Grade									
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Thrombocytopenia	24 (7.3)	7 (2.1)	8 (2.4)	2 (0.6)	41 (12.5)	2 (1.2)	2 (1.2)	1 (0.6)	0	5 (3.1)
Dyspnea	27 (8.3)	10 (3.1)	2 (0.6)	1 (0.3)	40 (12.2)	5 (3.1)	5 (3.1)	1 (0.6)	0	11 (6.8)
Influenza-like illness	29 (8.9)	10 (3.1)	0	0	39 (11.9)	10 (6.2)	5 (3.1)	0	0	15 (9.3)
Urinary tract infection	0	30 (9.2)	6 (1.8)	0	36 (11.0)	0	16 (9.9)	1 (0.6)	0	17 (10.6)
Weight decreased	20 (6.1)	13 (4.0)	3 (0.9)	NA	36 (11.0)	2 (1.2)	2 (1.2)	1 (0.6)	NA	5 (3.1)
Neuropathy	29 (8.9)	5 (1.5)	1 (0.3)	0	35 (10.7)	15 (9.3)	1 (0.6)	0	0	16 (9.9)
Pain in extremity	23 (7.0)	10 (3.1)	2 (0.6)	NA	35 (10.7)	11 (6.8)	8 (5.0)	0	NA	19 (11.8)
Bone pain	21 (6.4)	13 (4.0)	0	0	34 (10.4)	7 (4.3)	7 (4.3)	0	0	14 (8.7)
Myalgia	29 (8.9)	5 (1.5)	0	0	34 (10.4)	9 (5.6)	3 (1.9)	0	0	12 (7.5)
Pyrexia	30 (9.2)	3 (0.9)	1 (0.3)	0	34 (10.4)	13 (8.1)	4 (2.5)	0	0	17 (10.6)
Hot flush	26 (8.0)	7 (2.1)	0	NA	33 (10.1)	24 (14.9)	4 (2.5)	0	NA	28 (17.4)
Edema peripheral	26 (8.0)	7 (2.1)	0	0	33 (10.1)	9 (5.6)	1 (0.6)	0	0	10 (6.2)
Upper respiratory tract infection	1 (0.3)	32 (9.8)	0	0	33 (10.1)	0	9 (5.6)	0	0	9 (5.6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; n = number of patients within category; NA = not applicable per CTCAE; NSAI = nonsteroidal aromatase inhibitor; TEAE = treatment-emergent adverse event.

Source: ae_pt_345.rtf.

The most common TEAEs regardless of severity (by≥ 10% of the patients) in the experimental arm are diarrhoea (82 %), neutropenia (44 %), fatigue (41 %), nausea (41 %), anaemia (32 %), abdominal pain (31 %), vomiting (30 %) and alopecia (28 %).

A higher percentage of TEAEs considered treatment related was reported for patients in the abemaciclib containing arm (95 %) compared to the control arm (57 %).

Grade 3 TEAEs were reported for 169 patients (52 %) and Grade 4 TEAEs for 2 patients (7 %) including neutropenia (1.8 %), hyponatremia (~ 1 %), embolism (0.6%) and GGT increased (0.3 %).

In contrast to the safety profiles of the two approved CDK4/6 inhibitors palbociclib (Ibrance) and ribociclib (Kisqali) where neutropenia was the most commonly reported AE (81 % [55 % Grad 3] and 74 % [60 % Grad 3/4] respectively), with abemaciclib it is diarrhoea (82 % with ~10 % Grade 3) whilst neutropenia is reported to quite a lesser extent (4 % with 22 % Grade 3 and 2 % Grade 4).

Serious adverse event / deaths / other significant events

Serious adverse events

SAEs were reported in 102 (31.2 %) of the abemaciclib treated patients (compared to 27 (16.8 %) in the control arm). The most common reason for a SAE report in the abemaciclib containing arm was lung infection (4 % whilst none in the control arm) followed by embolism which accounted for 2.4 % in the experimental arm compared to 0.6 % in control arm. Anaemia was reported in 1.8%, and diarrhoea in 1.5 %. There were five (1.5 %) SAE reports of acute kidney injury.

Hospitalizations

About 21 % of all patients in the safety population reported ≥1 hospitalization with the vast majority (21 %) due to TEAEs (78 patients [24 %] in the experimental arm and 23 patients [14 %] in the control arm). The most common TEAEs for abemaciclib-treated patients were lung infection (8 patients [~ 2 %]), embolism (7 patients [2 %]), and diarrhoea (4 patients [~ 1 %]).

The median duration of hospitalization was 10 days (range 1 to 504) for the abemaciclib-treated patients and 6 days (range 2 to 67 days) for the placebo-treated patients.

Deaths

Deaths on therapy or within 30 days of treatment discontinuation were reported for 15 patients (4.6%) in the experimental arm including 11 patients (3.4%) due to AEs and 4 patients (~1 %) due to study disease. The most common AE by preferred term resulting in death in the abemaciclib containing arm was lung infection (1.2 %) and embolism (2 patients [0.6 %]).

A total of 74 deaths (15 %) occurred after 30 days of treatment discontinuation (14.7 % in the experimental arm and 16.1 % in the control arm). All these cases were attributed to study disease.

Laboratory findings

Summary of Treatment-Emergent Maximum Post-baseline CTCAE Laboratory Abnormalities Based on Central Laboratory Analysis CTCAE Term by Decreasing Frequency in the Abemaciclib Plus NSAI Arm Safety Population

	Abemaciclib + NSAI N=327						Placebo + NSAI N=161					
	CTCAE Grade											
	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Patients with ≥1 CTCAE term	316	25 (7.9)	137 (43.4)	131 (41.5)	22 (7.0)	315 (99.7)	158	93 (58.9)	41 (25.9)	15 (9.5)	1 (0.6)	150 (94.9)
Creatinine increased[a,b]	314	126 (40.1)	173 (55.1)	9 (2.9)	0	308 (98.1)	156	126 (80.8)	7 (4.5)	0	0	133 (85.3)
Anemia	313	128 (40.9)	128 (40.9)	6 (1.9)	0	262 (83.7)	156	34 (21.8)	18 (11.5)	0	0	52 (33.3)
WBC decreased	313	81 (25.9)	132 (42.2)	47 (15.0)	0	260 (83.1)	156	34 (21.8)	13 (8.3)	1 (0.6)	0	48 (30.8)
Neutrophil count decreased	313	59 (18.8)	121 (38.7)	63 (20.1)	9 (2.9)	252 (80.5)	156	25 (16.0)	6 (3.8)	4 (2.6)	0	35 (22.4)
Lymphocyte count decreased	313	81 (25.9)	69 (22.0)	29 (9.3)	2 (0.6)	181 (57.8)	156	21 (13.5)	18 (11.5)	3 (1.9)	0	42 (26.9)
ALT increased	313	106 (33.9)	36 (11.5)	23 (7.3)	2 (0.6)	167 (53.4)	155	37 (23.9)	3 (1.9)	3 (1.9)	0	43 (27.7)
AST increased	313	109 (34.8)	16 (5.1)	14 (4.5)	0	139 (44.4)	155	33 (21.3)	6 (3.9)	1 (0.6)	0	40 (25.8)
Platelet count decreased	312	107 (34.3)	11 (3.5)	4 (1.3)	2 (0.6)	124 (39.7)	155	20 (12.9)	0	1 (0.6)	0	21 (13.5)

Continued

	Abemaciclib + NSAI N=327						Placebo + NSAI N=161					
	CTCAE Grade											
	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Hyponatremia	314	84 (26.8)	0	17 (5.4)	1 (0.3)	102 (32.5)	156	39 (25.0)	0	0	0	39 (25.0)
Hypercalcemia	314	97 (30.9)	1 (0.3)	0	2 (0.6)	100 (31.8)	156	50 (32.1)	1 (0.6)	0	0	51 (32.7)
Hypokalemia	314	73 (23.2)	0	24 (7.6)	1 (0.3)	98 (31.2)	155	20 (12.9)	0	0	0	20 (12.9)
Hypocalcemia	314	73 (23.2)	13 (4.1)	1 (0.3)	2 (0.6)	89 (28.3)	156	28 (17.9)	4 (2.6)	0	1 (0.6)	33 (21.2)
Alkaline phosphatase increased	314	50 (15.9)	12 (3.8)	1 (0.3)	0	63 (20.1)	156	20 (12.8)	3 (1.9)	2 (1.3)	0	25 (16.0)
Hyperkalemia	314	18 (5.7)	12 (3.8)	0	3 (1.0)	33 (10.5)	155	3 (1.9)	3 (1.9)	2 (1.3)	0	8 (5.2)
Hypoalbuminemia	314	11 (3.5)	8 (2.5)	0	0	19 (6.1)	156	2 (1.3)	1 (0.6)	0	0	3 (1.9)
Blood bilirubin increased	313	11 (3.5)	5 (1.6)	1 (0.3)	0	17 (5.4)	155	8 (5.2)	2 (1.3)	0	0	10 (6.5)
Hypernatremia	314	15 (4.8)	0	0	0	15 (4.8)	156	5 (3.2)	0	0	0	5 (3.2)
Lymphocyte count increased	313	0	4 (1.3)	0	0	4 (1.3)	156	0	0	0	0	0
Hemoglobin increased	313	3 (1.0)	0	0	0	3 (1.0)	156	7 (4.5)	0	0	0	7 (4.5)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events, version 4.0; MATE = multidrug and toxin extrusion protein; N = number of patients in the safety population; n = number of patients with graded laboratory value; N1 = number of patients with at least a baseline result and 1 postbaseline result, used as denominators for the percentages; NSAI = nonsteroidal aromatase inhibitor; OCT2 = organic cation transporter 2; ULN = upper limit of normal; WBC = white blood cell.

[a] Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine (inhibitor of OCT2, MATE1, and MATE2-K) without affecting glomerular function.

[b] CTCAE version 4.0 defines Grade 1 creatinine increased as >1 - 1.5 x baseline or >ULN - 1.5 x ULN.

Source: t_lab_bymaxgrad_s.rtf.

The high incidence of laboratory abnormality reports of neutropenia, anaemia and thrombocytopenia reflects the CDK 4/6 inhibitor mode of action and thus is not unexpected. There are some differences in regard to electrolytes between the abemaciclib treated patients and patients in the control arm. Given the high incidence

of diarrhoea and vomiting associated with abemaciclib treatment which may lead to dehydration, further details have revealed that in the majority of reports of ≥ 3 hyponatremia and ≥ 3 hypokalaemia a temporal association with diarrhoea, vomiting and with dehydration was demonstrated.

Safety in special populations

Gender

N/A as all patients were females.

Race

There were in total 58.4 % Caucasian patients enrolled (56.6 % in the experimental arm and 62.1 % in the control arm) as compared to 30.3 % Asian patients (31.5 % and 28.0 % in the respective arms). Others were Black or African American (8 [1.6 %]), American Indian or Alaska Native (6 [1.2 %]). These numbers are however considered too limited to draw any conclusions.

Overall, Asian patients experienced more TEAEs as compared to the Caucasian population which included neutropenia, anaemia, ALT/ AST increases (Grade≥3 neutropenia: 27.2% in Asian patients and 16.8% in Caucasian patients; Grade≥3 anaemia 9.7% and 3.8% respectively; ALT TEAEs: 12.6% in Asian patients, 3.2% in Caucasian patients; ALT laboratory abnormalities: 14.9% versus 2.9% in Caucasian patients; AST TEAEs: 7.8% versus 1.6%; AST laboratory abnormalities: 9.9% versus 1.1% in Caucasian patients. However, a higher incidence in Caucasian patients (11.9%) compared to that of Asian patients (4.9%) were noted for events of Grade ≥3 diarrhoea.

Age

No relevant differences in the incidence of TEAEs of diarrhoea, neutropenia, increased liver enzymes or the overall infections and infestations SOC were observed between the age groups. Patients aged ≥ 65 years as compared to patients < 65 years reported however more lymphopenia (lymphocyte count decreased 57.9% versus 48.6%, respectively), thrombocytopenia (platelet count decreased across all grades 48.9% versus 26.0% respectively), hypokalaemia, hypocalcaemia, decreased appetite, and blood creatinine increased. Furthermore, an overall higher rate of events in the Infections and Infestations SOC in patients aged ⩾65 years than in patients aged <65 years (50.0% and 40.8% respectively). The majority of events were low grade; ⩾ Grade 3 infections occurred more frequently in patients aged ⩾65 years (11.5%) than in patients aged <65 years (5.6%). However, no particular infection drove this difference.

Safety in Special Populations

MONARCH 3

MedDRA Term:	Age <65 N=179 n (%)	Age 65-74 N=106 n (%)	Age 75-84 N=37 n (%)	Age 85+ N=5 n (%)
Total AEs	177 (98.9)	105 (99.1)	36 (97.3)	5 (100.0)
Serious AEs				
Total	38 (21.2)	38 (35.8)	22 (59.5)	4 (80.0)
Fatal	5 (2.8)	4 (3.8)	2 (5.4)	0
Hospitalization/prolong existing hospitalization	35 (19.6)	36 (34.0)	21 (56.8)	4 (80.0)
Life-threatening	7 (3.9)	7 (6.6)	8 (21.6)	1 (20.0)
Disability/incapacity	6 (3.4)	3 (2.8)	1 (2.7)	0
Other (medically significant)	7 (3.9)	4 (3.8)	5 (13.5)	1 (20.0)
AE leading to drop-out[a]	21 (11.7)	20 (18.9)	11 (29.7)	1 (20.0)
Psychiatric disorders[b]	25 (14.0)	20 (18.9)	5 (13.5)	1 (20.0)
Nervous system disorders[b]	76 (42.5)	52 (49.1)	13 (35.1)	3 (60.0)
Accidents and injuries[c]	18 (10.1)	17 (16.0)	6 (16.2)	1 (20.0)
Cardiac disorders[b]	14 (7.8)	12 (11.3)	7 (18.9)	1 (20.0)
Vascular disorders[b]	33 (18.4)	43 (40.6)	11 (29.7)	3 (60.0)
Cerebrovascular disorders[d]	3 (1.7)	3 (2.8)	2 (5.4)	0
Infections and infestations[b]	73 (40.8)	53 (50.0)	17 (45.9)	4 (80.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[e]	33 (18.4)	24 (22.6)	8 (21.6)	1 (20.0)
Other AE appearing more frequently in older patients	See Table 6.3			

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in population; n = number of patients in category; SMQ = standardised MedDRA query.

a AEs leading to drop-out: discontinuation of study treatment.

b For Psychiatric disorders, Nervous system disorders, Cardiac disorders, Vascular disorders, Infections and infestations: MedDRA System Organ Class.

c Accidents and injuries: MedDRA SMQ Accidents and Injuries 20000135.

d Cerebrovascular disorders: MedDRA SMQ Cerebrovascular Disorders 20000060.

e Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures: summary of respective MedDRA preferred terms.

Source: ems_tease_age_select1.

Discontinuation due to adverse events

Fifty-four patients (17 %) in the abemaciclib arm discontinued study treatment due to AEs and 5 patients (3 %) in the control arm. AEs reported as the reason for study treatment discontinuation in > 1% of the patients in the abemaciclib arm were ALT increased and lung infection (6 patients [1.8 %] each), diarrhoea and embolism (4 patients [1.2%] each).

Of the patients who discontinued any study drug, 31 patients (9 %) in the abemaciclib arm first discontinued from abemaciclib treatment due to an AE and continued treatment with the NSAI.

The proportion of discontinuation due to AEs does not raise any concern at this point.

MONARCH 2 (abemaciclib plus fulvestrant)

The Phase III MONARCH 2 study enrolled patients with HR+, HER2- mBC who had disease progression following endocrine therapy. A total of 664 patients were randomized in a 2:1 design with 441 patients in the experimental arm and 223 in the placebo arm.

Notably, the original MONARCH 2 protocol was amended (JPBL[a]) to change the starting dose of blinded study drug (abemaciclib from 200-mg Q12H to 150-mg Q12H or placebo) in order to improve tolerability i.e. primarily diarrhoea occurring during the first treatment cycle, observed in blinded safety review of MONARCH 2 and in studies JPBA and JPBH. All ongoing 200 mg Q12H patients were shifted to 150 mg Q12H.

Data cut-off date 14 February 2017

Patient exposure

Duration of therapy was longer in the experimental as compared to the control arm (13 months and 9 months respectively) with a median number of cycles of abemaciclib received per patient of 13 as compared to 9 cycles in the control arm. The median number of cycles of fulvestrant received per patient was 15 and 9 cycles in the respective arms. A difference in dose intensity between the two arms is observed (median 273 mg/day and mean 261 mg/day in the experimental arm versus median 298 mg/day and mean 309 mg/day in the control arm).

Dose Adjustments and Omissions

A total of 49.4 % had abemaciclib dose reductions with the majority due to AEs (189 patients [42.9%]). Most common AEs included diarrhoea (83 patients [18.8%]) and neutropenia (44 patients [10.0%]). About 58.0% had at least one abemaciclib dose omission with 51.9 % due to AEs which included diarrhoea (83 patients [18.8%]) and neutropenia (72 patients [16.3%]). It is noted that 21.1 % required ≥ 3 dose omissions.

The median number of days that patients were treated with abemaciclib at 200 mg or 150 mg twice a day prior to discontinuation or dose reduction for any reason (including disease progression) was 34 days and 92 days, respectively. For the overall safety population, the median number of days to the first dose reduction due to diarrhoea was 29 days. The median number of days to the first dose reduction due to diarrhoea was 16.5 days and 38 days for patients treated with abemaciclib at 200 mg or 150 mg twice a day, respectively.

Adverse events

Overview of AEs, Safety Population MONARCH 2

	Number (%) of Patients	
Number of Patients[a]	Abemaciclib + Fulvestrant N=441	Placebo + Fulvestrant N=223
Patients with ≥1 TEAE	435 (98.6)	199 (89.2)
Related to study treatment[b]	420 (95.2)	134 (60.1)
Patients with ≥1 CTCAE ≥Grade 3 TEAE	276 (62.6)	53 (23.8)
Related to study treatment[b]	232 (52.6)	13 (5.8)
Patients with ≥1 SAE	99 (22.4)	24 (10.8)
Related to study treatment[b]	39 (8.8)	3 (1.3)
Patients who discontinued study treatment due to an AE[c]	38 (8.6)	7 (3.1)
Related to study treatment[b]	30 (6.8)	4 (1.8)
Patients who discontinued study treatment due to an SAE[c]	18 (4.1)	3 (1.3)
Related to study treatment[b]	12 (2.7)	0
Patients who died due to an AE on study treatment[d]	6 (1.4)	1 (0.4)
Related to study treatment[b]	4[d] (0.9)	0
Patients who died due to an AE within 30 days of discontinuation from study treatment[e]	3 (0.7)	1 (0.4)
Related to study treatment[b]	1 (0.2)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the safety population; n = number of patients in the specified category; SAE = serious adverse events; TEAE = treatment-emergent adverse event.

a Patients may be counted in >1 category.

b Includes events that were considered related to study treatment (either abemaciclib/placebo or fulvestrant) as judged by the investigator.

c Patients who died on study treatment with primary cause as AE or SAE are also included as discontinuations.

d The death due to AE for Patient 1687 was not considered related by the investigator in the clinical database. However, in the information submitted to the Lilly Safety System database, the investigator indicated that this death was related to blinded study drug.

e Deaths are also included as SAEs and discontinuations due to AEs.

This is basically the same distribution as observed in MONARCH 3 suggesting that the safety profile of abemaciclib is not likely to alter to any major extent regardless of endocrine therapy.

TEAEs by Maximum CTCAE Grade Experienced by ≥ 10% of Population in Either Arm Preferred Term by Decreasing Frequency (All Grades) in the Abemaciclib Plus Fulvestrant Arm, Safety Population

	Abemaciclib + Fulvestrant N=441					Placebo + Fulvestrant N=223				
	CTCAE Grade									
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Patients with ≥1 TEAE, n (%)	26 (5.9)	133 (30.2)	241 (54.6)	26 (5.9)	435 (98.6)	64 (28.7)	82 (36.8)	46 (20.6)	5 (2.2)	199 (89.2)
Diarrhea	182 (41.3)	140 (31.7)	59 (13.4)	0	381 (86.4)	43 (19.3)	11 (4.9)	1 (0.4)	0	55 (24.7)
Neutropenia	23 (5.2)	63 (14.3)	104 (23.6)	13 (2.9)	203 (46.0)	4 (1.8)	1 (0.4)	3 (1.3)	1 (0.4)	9 (4.0)
Nausea	129 (29.3)	58 (13.2)	12 (2.7)	NA	199 (45.1)	38 (17.0)	11 (4.9)	2 (0.9)	NA	51 (22.9)
Fatigue	100 (22.7)	64 (14.5)	12 (2.7)	NA	176 (39.9)	48 (21.5)	11 (4.9)	1 (0.4)	NA	60 (26.9)
Abdominal pain	103 (23.4)	42 (9.5)	11 (2.5)	NA	156 (35.4)	24 (10.8)	9 (4.0)	2 (0.9)	NA	35 (15.7)
Anemia	29 (6.6)	67 (15.2)	31 (7.0)	1 (0.2)	128 (29.0)	4 (1.8)	2 (0.9)	2 (0.9)	0	8 (3.6)
Leukopenia	24 (5.4)	62 (14.1)	38 (8.6)	1 (0.2)	125 (28.3)	2 (0.9)	2 (0.9)	0	0	4 (1.8)
Decreased appetite	69 (15.6)	43 (9.8)	5 (1.1)	0	117 (26.5)	23 (10.3)	2 (0.9)	1 (0.4)	0	27 (12.1)
Vomiting	79 (17.9)	31 (7.0)	4 (0.9)	0	114 (25.9)	15 (6.7)	4 (1.8)	4 (1.8)	0	23 (10.3)
Headache	62 (14.1)	24 (5.4)	3 (0.7)	NA	89 (20.2)	23 (10.3)	10 (4.5)	1 (0.4)	NA	34 (15.2)
Dysgeusia	60 (13.6)	19 (4.3)	NA	NA	79 (17.9)	5 (2.2)	1 (0.4)	NA	NA	6 (2.7)
Alopecia	60 (13.6)	9 (2.0)	NA	NA	69 (15.9)	4 (1.8)	0	NA	NA	4 (1.8)
Thrombocytopenia	35 (7.9)	19 (4.3)	9 (2.0)	6 (1.4)	69 (15.6)	4 (1.8)	1 (0.4)	0	1 (0.4)	6 (2.7)
Stomatitis	48 (10.9)	17 (3.9)	2 (0.5)	0	67 (15.2)	18 (8.1)	5 (2.2)	0	0	23 (10.3)
Constipation	47 (10.7)	10 (2.3)	3 (0.7)	0	60 (13.6)	26 (11.7)	3 (1.3)	1 (0.4)	0	30 (13.5)
ALT increased	23 (5.2)	18 (4.1)	17 (3.9)	1 (0.2)	59 (13.4)	5 (2.2)	3 (1.3)	4 (1.8)	0	12 (5.4)
Cough	44 (10.0)	15 (3.4)	0	NA	59 (13.4)	21 (9.4)	4 (1.8)	0	NA	25 (11.2)
Pruritus	49 (11.1)	8 (1.8)	0	NA	57 (12.9)	12 (5.4)	1 (0.4)	0	NA	13 (5.8)
Dizziness	45 (10.2)	7 (1.6)	3 (0.7)	NA	55 (12.5)	11 (4.9)	2 (0.9)	0	NA	13 (5.8)
AST increased	25 (5.7)	19 (4.3)	10 (2.3)	0	54 (12.2)	7 (3.1)	2 (0.9)	6 (2.7)	0	15 (6.7)
Blood creatinine increased	27 (6.1)	21 (4.8)	4 (0.9)	0	52 (11.8)	1 (0.4)	0	0	0	1 (0.4)

Continued

	Abemaciclib + Fulvestrant N=441					Placebo + Fulvestrant N=223				
	CTCAE Grade									
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Arthralgia	34 (7.7)	16 (3.6)	1 (0.2)	NA	51 (11.6)	24 (10.8)	7 (3.1)	1 (0.4)	NA	32 (14.3)
Oedema peripheral	41 (9.3)	10 (2.3)	0	NA	51 (11.6)	12 (5.4)	3 (1.3)	0	NA	15 (6.7)
Rash	35 (7.9)	9 (2.0)	5 (1.1)	0	49 (11.1)	8 (3.6)	2 (0.9)	0	0	10 (4.5)
Upper respiratory tract infection	NA	49 (11.1)	0	0	49 (11.1)	1 (0.4)	14 (6.3)	2 (0.9)	0	17 (7.6)
Dyspnea	22 (5.0)	14 (3.2)	11 (2.5)	1(0.2)	48 (10.9)	15 (6.7)	7 (3.1)	3 (1.3)	0	25 (11.2)
Pyrexia	38 (8.6)	7 (1.6)	2 (0.5)	1 (0.2)	48 (10.9)	10 (4.5)	2 (0.9)	1 (0.4)	0	13 (5.8)
Muscular weakness	23 (5.2)	20 (4.5)	4 (0.9)	NA	47 (10.7)	10 (4.5)	3 (1.3)	0	NA	13 (5.8)
Hot flush	39 (8.8)	7 (1.6)	0	NA	46 (10.4)	15 (6.7)	7 (3.1)	0	NA	22 (9.9)
Weight decreased	22 (5.0)	23 (5.2)	1 (0.2)	NA	46 (10.4)	3 (1.3)	1 (0.4)	1 (0.4)	NA	5 (2.2)
Back pain	24 (5.4)	15 (3.4)	3 (0.7)	NA	42 (9.5)	14 (6.3)	12 (5.4)	2 (0.9)	NA	28 (12.6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; NA = not applicable per CTCAE; N = number of patients in the safety population; n = number of patients in the specified category; TEAE = treatment-emergent adverse event.

Source: home/lillyce/prd/ly2835219/i3y_mc_jpbl/csr1/programs_nonsdd/tfl_output/ ae_pt_345_ly.rtf

The distribution and proportions of TEAEs including by severity is very similar to that observed in MONARCH 3. Most common TEAEs regardless of severity (by≥10% of the patients) in the experimental arm are diarrhoea (86 %), neutropenia (46 %), nausea (45 %), fatigue (40 %), abdominal pain (35 %), anemia (29 %), leukopenia (28 %), vomiting (26 %), headache (20 %) and alopecia (16 %). Corresponding proportions in MONARCH 3 were diarrhoea (81 %), neutropenia (41 %), fatigue (40 %), nausea (39 %), abdominal pain (29 %), anemia (28 %), vomiting (28 %), and alopecia (27 %).

Grade 3 TEAEs were reported for 241 patients (55 %) and Grade 4 TEAEs for 26 patients (6 %) including neutropenia (3 %) and thrombocytopenia (1.4 %) in the MONARCH 2 study.

Endocrine-Naïve Population

The original **MONARCH 2** protocol allowed patients who presented de novo with locally advanced or metastatic disease and not received any prior endocrine therapy. Based on regulatory advice from the FDA however, the protocol was amended to remove the endocrine therapy naive patients from the ITT population to reduce heterogeneity. A total of 43 patients were included (27 patients received abemaciclib plus fulvestrant and 16 patients received placebo plus fulvestrant). It is recognised that overall, the safety profile of abemaciclib + fulvestrant in the endocrine-naïve population appears similar to the endocrine pre-treated population. Due to the limited sample size however, no detailed conclusions can be drawn. Any major difference in terms of tolerability concerns for abemaciclib + fulvestrant given as 1st line or as 2nd line population is not anticipated.

Serious adverse events and deaths

Serious adverse events

Treatment-Emergent Serious Adverse Events Occurring in ≥ 1% of Patients in Either Arm, Preferred Term by Decreasing Frequency in the Abemaciclib Plus Fulvestrant Arm Safety Population

Preferred Term Reported Term	Abemaciclib + Fulvestrant N=441 n (%)	Placebo + Fulvestrant N=223 n (%)
Patients with ≥1 serious adverse event	99 (22.4)	24 (10.8)
Embolism	9 (2.0)	1 (0.4)
Pulmonary embolism	3	0
DVT	2	1
Acute DVT of inferior vena cava	1	0
Pulmonary thromboembolism	1	0
Cerebral venous sinus thrombosis	1	0
Cerebral infarction	1	0
Diarrhea	7 (1.6)	0
Lung infection	7 (1.6)	0
Pneumonia	3	0
Lung infection	1	0
Bilateral pneumonia	1	0
Community-acquired bacterial pneumonia	1	0
Cryptogenic organizing pneumonia	1	0
Dyspnea	6 (1.4)	2 (0.9)
Dyspnea[a]	5	2
Shortness of breath[a]	1	0
Persistent cough	1	0
Sepsis	6 (1.4)	1 (0.4)
Septic shock	4	0
Sepsis	2	0
Intra-abdominal sepsis	0	1
Abdominal pain	5 (1.1)	1 (0.4)
Abdominal pain	3	1
Abdominal pain secondary to cecal volvulus	1	0
Pain: abdominal	1	0
Nausea	5 (1.1)	1 (0.4)
Pleural effusion	2 (0.5)	5 (2.2)
Pleural effusion	1	3
Large left pleural effusion	1	0
Left hydrothorax	0	1
Bilateral pleural effusions	0	1

Abbreviations: DVT = deep vein thrombosis; N = number of patients in the population; n = number of patients with a serious adverse event.

[a] One patient had both dyspnea and shortness of breath reported on the same day.

Source: home/lillyce/prd/ly2835219/i3y_mc_jpbl/misc3/programs_nonsdd/tfl_output/c_ae_serious_pt_lp.rtf and sae_o_ae_1_all_ae.rtf.

Again the similarity with MONARCH 3 is recognised. About 22 % had ≥ 1 SAE in MONARCH 2 and 28 % in MONARCH 3. The number of reports is also similar in regard to embolism and diarrhoea.

Hospitalizations

A total of 117 patients (18 %) reported ≥1 hospitalization including 93 patients (21 %) in the experimental arm and 24 patients (11 %) in the control arm.

The median duration of hospitalization was eight days and the median number of admissions per patient was one. The most common TEAEs leading to hospitalization for patients in the abemaciclib containing arm were dyspnoea (7 patients [~ 2 %]), embolism (6 patients [1.4%]), lung infection (5 patients [1 %]), and sepsis (5 patients [1 %]).

Similarity with MONARCH 3 is recognised**.** In MONARCH 3 a total of about 77 (16 %) reported ≥ 1 hospitalization (59 [18 %] in the experimental arm). Similarity is also observed in terms of reasons for hospitalization.

Deaths

Summary of Deaths on Therapy or Within 30 Days of Treatment Discontinuation, Safety Population

	Abemaciclib + Fulvestrant N=441 n (%)	Placebo + Fulvestrant N=223 n (%)
All deaths	84 (19.0)	48 (21.5)
Deaths on therapy or within 30 days of treatment discontinuation	**14 (3.2)**	**10 (4.5)**
Reasons for death		
Adverse events	9 (2.0)	2 (0.9)
Sepsis	3 (0.7)	0
Embolism[a]	1 (0.2)	0
Hepatic failure	1 (0.2)	0
Hepatic function abnormal	1 (0.2)	0
Lung infection[b]	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.2)	0
Pneumonitis	1 (0.2)	0
Decreased appetite	0	1 (0.4)
Cardiac arrest	0	1 (0.4)
Study disease	5 (1.1)	7 (3.1)
Not reported	0	1 (0.4)[c]

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in the population; n = number of patients in the specified category.

[a] Cerebral infarct coded as embolism per CTCAE term.

[b] Cryptogenic organizing pneumonia coded as lung infection per CTCAE term.

[c] The patient died after discontinuation from treatment due to progressive disease. No further information on the cause of death is available.

Source: o_ds_death_by_reason_4_ly.rtf.

Deaths on therapy or within 30 days of treatment discontinuation were reported for 14 patients (3 %) in the experimental arm including 9 patients (2 %) due to AEs and 5 patients (1 %) due to study disease. The most common AE by preferred term resulting in death in the abemaciclib containing arm was sepsis (0.7 %). The number of deaths due to AEs (2 %) does not *per se* raise concerns at this point.

Laboratory findings

Summary of Treatment-Emergent Maximum Post-baseline CTCAE Laboratory Abnormalities Based on Central Laboratory Analysis CTCAE Term by Decreasing Frequency in the Abemaciclib Plus Fulvestrant Arm Safety Population MONARCH 2

	Abemaciclib + Fulvestrant N=441 n (%)						Placebo + Fulvestrant N=223 n (%)					
	CTCAE Grade						CTCAE Grade					
	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Patients with ≥1 CTCAE term	434	41 (9.4)	178 (41.0)	187 (43.1)	28 (6.5)	434 (100)	219	127 (58.0)	62 (28.3)	23 (10.5)	4 (1.8)	216 (98.6)
Creatinine increased[a,b]	434	231 (53.2)	191 (44.0)	5 (1.2)	0	427 (98.4)	219	154 (70.3)	7 (3.2)	0	0	161 (73.5)
White blood cell count decreased	426	103 (24.2)	182 (42.7)	96 (22.5)	3 (0.7)	384 (90.1)	218	46 (21.1)	23 (10.6)	2 (0.9)	0	71 (32.6)
Neutrophil count decreased	426	73 (17.1)	161 (37.8)	122 (28.6)	15 (3.5)	371 (87.1)	218	41 (18.8)	16 (7.3)	8 (3.7)	1 (0.5)	66 (30.3)
Anemia	426	140 (32.9)	206 (48.4)	11 (2.6)	0	357 (83.8)	218	55 (25.2)	17 (7.8)	1 (0.5)	0	73 (33.5)
Lymphocyte count decreased	426	110 (25.8)	106 (24.9)	51 (12.0)	1 (0.2)	268 (62.9)	218	40 (18.3)	25 (11.5)	4 (1.8)	0	69 (31.7)
Platelet count decreased	425	188 (44.2)	29 (6.8)	4 (0.9)	5 (1.2)	226 (53.2)	218	30 (13.8)	2 (0.9)	0	0	32 (14.7)
Alanine aminotransferase increased	434	123 (28.3)	35 (8.1)	17 (3.9)	3 (0.7)	178 (41.0)	219	59 (26.9)	9 (4.1)	3 (1.4)	0	71 (32.4)
Aspartate aminotransferase increased	433	130 (30.0)	15 (3.5)	17 (3.9)	0	162 (37.4)	219	41 (18.7)	5 (2.3)	8 (3.7)	1 (0.5)	55 (25.1)
Hyponatremia	434	136 (31.3)	0	17 (3.9)	0	153 (35.3)	219	56 (25.6)	0	6 (2.7)	0	62 (28.3)

Continued

	Abemaciclib + Fulvestrant N=441 n (%)						Placebo + Fulvestrant N=223 n (%)					
	CTCAE Grade						CTCAE Grade					
	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	N1	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Hypokalemia	434	115 (26.5)	0	30 (6.9)	1 (0.2)	146 (33.6)	219	24 (11.0)	0	1 (0.5)	0	25 (11.4)
Hypercalcemia	434	127 (29.3)	3 (0.7)	1 (0.2)	1 (0.2)	132 (30.4)	219	68 (31.1)	0	1 (0.5)	1 (0.5)	70 (32.0)
Hypocalcemia	434	81 (18.7)	19 (4.4)	2 (0.5)	3 (0.7)	105 (24.2)	219	36 (16.4)	7 (3.2)	0	0	43 (19.6)
Alkaline phosphatase increased	434	53 (12.2)	21 (4.8)	4 (0.9)	0	78 (18.0)	219	25 (11.4)	10 (4.6)	3 (1.4)	0	38 (17.4)
Hypoalbuminemia	434	46 (10.6)	14 (3.2)	0	0	60 (13.8)	219	10 (4.6)	10 (4.6)	0	0	20 (9.1)
Hyperkalemia	434	22 (5.1)	5 (1.2)	3 (0.7)	1 (0.2)	31 (7.1)	219	20 (9.1)	5 (2.3)	1 (0.5)	0	26 (11.9)
Hypernatremia	434	15 (3.5)	0	0	0	15 (3.5)	219	5 (2.3)	0	0	0	5 (2.3)
Blood bilirubin increased	434	6 (1.4)	6 (1.4)	1 (0.2)	1 (0.2)	14 (3.2)	219	6 (2.7)	0	1 (0.5)	1 (0.5)	8 (3.7)
Lymphocyte count increased	426	0	4 (0.9)	0	0	4 (0.9)	218	0	3 (1.4)	0	0	3 (1.4)
Hemoglobin increased	426	1 (0.2)	0	1 (0.2)	0	2 (0.5)	218	12 (5.5)	0	0	0	12 (5.5)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, version 4.0; N = number of patients in the population; N1 = number of patients with at least a baseline result and 1 postbaseline result, used as denominators for the percentages; n = number of patients with graded laboratory value; ULN = upper limit of normal.

[a] Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine (inhibitor of organic cation transporter 2 [OCT2], multidrug and toxin extrusion protein 1 [MATE1], and MATE2-K) without affecting glomerular function.

[b] CTCAE version 4.0 defines Grade 1 creatinine increased as >1 - 1.5 x baseline or >ULN - 1.5 x ULN.

Source: lbmaxgrad_ly.rtf.

The laboratory abnormalities as observed in MONARCH 2 are very much in line with those in MONARCH 3.

Safety in special populations

Gender

N/A as this study enrolled exclusively women.

Race

There were in total 55.7 % Caucasian patients enrolled (53.1 % in the experimental arm and 61.0 % in the control arm) as compared to 32.1 % Asian patients (33.6 % and 29.1 % in the respective arms). Others were Black or African American (14 [2.1 %]), American Indian or Alaska Native (25 [3.8 %]).

As observed in MONARCH 3, Grade≥ 3 neutrophil count decreased and Grade≥ 3 neutropenia was higher in Asian patients than in non-Asian patients (neutrophil count decreased: 50.4% in Asian patients and 24.3% in non-Asian patients; neutropenia: 44.6% in Asian patients and 17.6% in non-Asian patients). Also Grade ≥ 3 elevated hepatic transaminases was higher in Asian patients than in non-Asian patients (ALT TEAEs: 6.8% in Asian patients and 2.7% in non-Asian patients; ALT laboratory abnormalities: 7.6% in Asian patients and 2.7% in non-Asian patients; AST TEAEs: 4.7% in Asian patients and 1.1% in non-Asian patients; AST laboratory abnormalities: 6.9% in Asian patients and 1.9% in non-Asian patients). As opposed to the findings in MONARCH 3, no major difference in the incidence of AEs of diarrhoea was observed.

Age

Overall, there is no major difference between patients < 65 (63.3) and ≥ 65 years (36.7 %) in terms of proportions of TEAE reports or according to severity.

MONARCH 2

MedDRA Term:	Age <65 N=287 n (%)	Age 65-74 N=113 n (%)	Age 75-84 N=38 n (%)	Age 85+ N=3 n (%)
Total AEs	283 (98.6)	111 (98.2)	38 (100.0)	3 (100.0)
Serious AEs				
Total	64 (22.3)	23 (20.4)	9 (23.7)	3 (100.0)
Fatal	6 (2.1)	2 (1.8)	1 (2.6)	0
Hospitalization/prolong existing hospitalization	61 (21.3)	22 (19.5)	9 (23.7)	3 (100.0)
Life-threatening	10 (3.5)	2 (1.8)	1 (2.6)	1 (33.3)
Disability/incapacity	3 (1.0)	2 (1.8)	1 (2.6)	0
Other (medically significant)	10 (3.5)	5 (4.4)	2 (5.3)	0
AE leading to drop-out[a]	20 (7.0)	10 (8.8)	8 (21.1)	0
Psychiatric disorders[b]	41 (14.3)	22 (19.5)	5 (13.2)	0
Nervous system disorders[b]	131 (45.6)	54 (47.8)	15 (39.5)	2 (66.7)
Accidents and injuries[c]	28 (9.8)	9 (8.0)	3 (7.9)	2 (66.7)
Cardiac disorders[b]	11 (3.8)	7 (6.2)	5 (13.2)	0
Vascular disorders[b]	74 (25.8)	23 (20.4)	9 (23.7)	2 (66.7)
Cerebrovascular disorders[d]	2 (0.7)	1 (0.9)	0	0
Infections and infestations[b]	128 (44.6)	11 (18.3)	14 (36.8)	1 (33.3)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[e]	35 (12.2)	25 (22.1)	6 (15.8)	2 (66.7)
Other AE appearing more frequently in older patients	See Table 6.4			

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in population; n = number of patients in category; SMQ = standardised MedDRA query.

a AEs leading to drop-out: discontinuation of study treatment.

b For Psychiatric disorders, Nervous system disorders, Cardiac disorders, Vascular disorders, Infections and infestations: MedDRA System Organ Class.

c Accidents and injuries: MedDRA SMQ Accidents and Injuries 20000135.

d Cerebrovascular disorders: MedDRA SMQ Cerebrovascular Disorders 20000060.

e Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures: summary of respective MedDRA preferred terms.

Source: tase_age_select1.

Discontinuations due to AEs

Thirty-eight patients (9 %) discontinued study treatment due to AEs in the experimental arm and 7 patients (3 %) in the control arm. The one AE reported in the abemaciclib containing arm as the reason for study treatment discontinuation for more than 1% of patients was diarrhoea (6 patients [1.4%]).

The discontinuation rate is considered acceptable and raises no concern at this point.

MONARCH 1 (JPBN.11.3, abemaciclib monotherapy)

The MONARCH 1 was a Phase II, single-arm, open-label study in patients with HR+, HER2- mBC whose disease had progressed on or after prior endocrine therapies and who previously received at least two chemotherapy regimens, one of which was in the metastatic setting were enrolled (N=132).

All enrolled patients were to receive 200 mg of abemaciclib orally BID on Days 1 to 28 of a 28-day cycle. The data cut-off date is 30 April 2016.

Patient exposure

The median number of cycles received per patient was 5 and the median and mean duration of therapy was about five and 7 months respectively. The median dose intensity was 357 mg/day and median relative dose intensity was 89 %.

Dose Adjustments and Omissions

The vast majority (100 patients [76 %]) had at least one dose adjustment with close to 50 % requiring a dose reduction and 72 % requiring dose omissions. The main reason for dose adjustments was diarrhoea (27 patients [21 %] requiring dose reductions and 32 patients [24 %] dose omissions) and neutropenia (14 patients [10 %] requiring dose reductions and 21 patients [16 %] omissions). The need for dose reductions occurred mainly in association with the two first cycles. The median time to first dose reduction was 39 days.

Adverse events

Overview of Adverse Events Enrolled Population MONARCH 1

	Number (%) of Patients
	Abemaciclib 200 mg
Number of Patients[a]	N = 132
Patients with ≥1 TEAE	132 (100.0)
Related to study treatment[b]	129 (97.7)
Patients with ≥1 SAE	32 (24.2)
Related to study treatment[b]	13 (9.8)
Patients who discontinued study treatment due to an AE	10 (7.6)
Related to study treatment[b]	8 (6.1)
Patients who discontinued study treatment due to an SAE	2 (1.5)
Related to study treatment[b]	1 (0.8)
Patients who died due to an AE on study treatment[c]	2 (1.5)
Related to study treatment[b]	1 (0.8)
Patients who died due to an AE within 30 days of discontinuation from study treatment[c]	1 (0.8)
Related to study treatment[b]	0

Abbreviations: AE = adverse event; N = number of patients in the Enrolled Population; n = number of patients in the specified category; SAE = serious adverse events; TEAE = treatment-emergent adverse events.

a Patients may be counted in more than 1 category.

b Includes events that were considered related to study treatment as judged by the investigator.

c Deaths are also included as SAEs and discontinuations due to AEs.

Source: o_ae_overview_p54281_t54300.

All patients reported ≥1 TEAE with almost all considered treatment related (98 %). About 24 % of the patients were reported having ≥ 1 SAE. As observed in MONARCH 1 and 2, this did however not translate into a corresponding high rate of treatment discontinuations due to AEs (~7 %).

Summary of TEAEs by Maximum CTCAE Grade experienced by ≥10% of the Population enrolled

	CTCAE Grade (N = 132)					
Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Patients with ≥ 1 event	7 (5.3)	35 (26.5)	75 (56.8)	12 (9.1)	3 (2.3)	132 (100.0)
Diarrhea	55 (41.7)	38 (28.8)	26 (19.7)	0	0	119 (90.2)
Fatigue	28 (21.2)	41 (31.1)	17 (12.9)	NA	NA	86 (65.2)
Nausea	52 (39.4)	27 (20.5)	6 (4.5)	NA	NA	85 (64.4)
Decreased appetite	37 (28.0)	19 (14.4)	4 (3.0)	0	0	60 (45.5)
Abdominal pain	29 (22.0)	19 (14.4)	3 (2.3)	NA	NA	51 (38.6)
Neutropenia	2 (1.5)	15 (11.4)	25 (18.9)	7 (5.3)	NA	49 (37.1)
Vomiting	30 (22.7)	14 (10.6)	2 (1.5)	0	0	46 (34.8)
Anemia	11 (8.3)	16 (12.1)	6 (4.5)	0	NA	33 (25.0)
Headache	18 (13.6)	9 (6.8)	0	NA	NA	27 (20.5)
Thrombocytopenia	13 (9.8)	9 (6.8)	5 (3.8)	0	NA	27 (20.5)
Pain	15 (11.4)	9 (6.8)	2 (1.5)	NA	NA	26 (19.7)
Cough	20 (15.2)	5 (3.8)	0	NA	NA	25 (18.9)
Constipation	17 (12.9)	5 (3.8)	1 (0.8)	0	NA	23 (17.4)
Leukopenia	3 (2.3)	12 (9.1)	7 (5.3)	1 (0.8)	0	23 (17.4)
Dyspnea	7 (5.3)	7 (5.3)	4 (3.0)	1 (0.8)	0	19 (14.4)
Dry mouth	16 (12.1)	2 (1.5)	0	NA	NA	18 (13.6)
Stomatitis	15 (11.4)	3 (2.3)	0	0	0	18 (13.6)
Weight decreased	13 (9.8)	5 (3.8)	0	NA	NA	18 (13.6)
Blood creatinine increased	6 (4.5)	10 (7.6)	1 (0.8)	0	NA	17 (12.9)
Alopecia	13 (9.8)	3 (2.3)	NA	NA	NA	16 (12.1)
Dysgeusia	14 (10.6)	2 (1.5)	NA	NA	NA	16 (12.1)
Back pain	9 (6.8)	5 (3.8)	1 (0.8)	NA	NA	15 (11.4)
Dizziness	13 (9.8)	2 (1.5)	0	NA	NA	15 (11.4)
Pyrexia	13 (9.8)	1 (0.8)	0	0	0	14 (10.6)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, version 4.0; N = number of patients in the population; n = number of patients in the specified category; NA = not applicable per CTCAE.
Source: teaeptmaxdose.rtf.

The most common TEAE associated with abemaciclib was diarrhoea which was reported in a substantial number of patients (89 % with 19 % Grade 3). Neutropenia is reported in 36 % with 19 % Grade 3 and 5 % Grade 4.

Serious adverse events and deaths

Serious adverse events

SAEs Preferred Term by Decreasing Frequency Enrolled Population

Preferred Term	Abemaciclib 200 mg N = 132 n (%)
Patients with ≥1 serious adverse event	32 (24.2)
Blood creatinine increased	4 (3.0)
Abdominal pain	3 (2.3)
Dehydration	3 (2.3)
Nausea	3 (2.3)
Dyspnoea	2 (1.5)
Embolism	2 (1.5)
Lung infection	2 (1.5)
Muscular weakness	2 (1.5)
Neutropenia	2 (1.5)
Pleural effusion	2 (1.5)
Acute kidney injury	1 (0.8)
Back pain	1 (0.8)
Bone pain	1 (0.8)
Conduction disorder	1 (0.8)
Constipation	1 (0.8)
Decreased appetite	1 (0.8)
Epilepsy	1 (0.8)
Fall	1 (0.8)
Febrile neutropenia	1 (0.8)
Gastroenteritis viral	1 (0.8)
Haematotoxicity	1 (0.8)
Hip fracture	1 (0.8)
Hypokalaemia	1 (0.8)
Intestinal obstruction	1 (0.8)
Leukopenia	1 (0.8)
Liver function test abnormal	1 (0.8)
Oesophageal varices haemorrhage	1 (0.8)
Pancreatitis	1 (0.8)
Pneumonitis	1 (0.8)
Pneumothorax	1 (0.8)
Pyrexia	1 (0.8)
Rash	1 (0.8)
Sepsis	1 (0.8)
Sinus bradycardia	1 (0.8)
Sinus tachycardia	1 (0.8)
Skin infection	1 (0.8)
Upper respiratory tract infection	1 (0.8)
Vomiting	1 (0.8)

Abbreviations: N = number of patients in the population; n = number of patients in the specified category.
Source: c_ae_serious_pt_p54281_t54301.

Given the very high rate of diarrhoea occurring in the study population (90 % with 20 % Grade 3) it is noted that none led to a SAE (albeit that dehydration is likely to be a result thereof). The one case each of febrile neutropenia and sepsis is also noted.

Hospitalizations

A total of 22 % were hospitalized due to AEs. Most commonly was blood creatinine increased (2.3%) followed by abdominal pain, dehydration and embolism (2 patients [1.5 %] each).

Median duration of hospitalization due to AEs was 6 days.

Deaths

Summary of Deaths Enrolled Population

	Abemaciclib 200 mg N = 132 n (%)
All Deaths	**47 (35.6)**
Deaths on therapy	**2 (1.5)**
Reason for death	
Adverse events	2 (1.5)
Pneumonitis	1 (0.8)
Sepsis	1 (0.8)
Adverse events related to study treatment	1 (0.8)
Pneumonitis	1 (0.8)
Deaths within 30 days of treatment discontinuation	**7 (5.3)**
Reason for death	
Study disease	6 (4.5)
Adverse events	1 (0.8)
Lung infection	1 (0.8)
Deaths after 30 days of treatment discontinuation	**38 (28.8)**
Reason for death	
Study disease	38 (28.8)

Abbreviations: N = number of patients in the population; n = number of patients in the specified category.
Source: o_ds_death_by_reason_p54281_t54286.

Two deaths occurred while on therapy, both due to AEs. In the case of the patient with sepsis, this was deemed related to procedure paracentesis with no evidence of neutropenia. In the case of pneumonitis, the investigator determined it to be possibly related to study drug. The majority of deaths either within or after 30 days of treatment discontinuation were attributed to the study disease.

Laboratory findings

Summary of Treatment-Emergent Maximum Post-baseline CTCAE Laboratory Abnormalities Based on Central Lab Analysis
CTCAE Term by Decreasing Frequency Enrolled Population

CTCAE Term	N1	CTCAE Grade (N = 132) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Patients with ≥1 CTCAE term	130	7 (5.4)	55 (42.3)	60 (46.2)	7 (5.4)	129 (99.2)
Creatinine increased	130	61 (46.9)	66 (50.8)	1 (0.8)	0	128 (98.5)
White blood cell decreased	130	24 (18.5)	58 (44.6)	36 (27.7)	0	118 (90.8)
Neutrophil count decreased	130	23 (17.7)	56 (43.1)	29 (22.3)	6 (4.6)	114 (87.7)
Anemia	130	39 (30.0)	50 (38.5)	0	0	89 (68.5)
Lymphocyte count decreased	130	6 (4.6)	31 (23.8)	17 (13.1)	1 (0.8)	55 (42.3)
Platelet count decreased	128	37 (28.9)	13 (10.2)	3 (2.3)	0	53 (41.4)
Alanine aminotransferase increased	130	30 (23.1)	6 (4.6)	4 (3.1)	0	40 (30.8)
Aspartate aminotransferase increased	130	32 (24.6)	2 (1.5)	5 (3.8)	0	39 (30.0)
Alkaline phosphatase increased	130	22 (16.9)	10 (7.7)	2 (1.5)	0	34 (26.2)
Hypokalemia	130	0	27 (20.8)	7 (5.4)	0	34 (26.2)
Hyponatremia	130	23 (17.7)	0	4 (3.1)	0	27 (20.8)
Hypoalbuminemia	130	15 (11.5)	7 (5.4)	0	0	22 (16.9)
Hypocalcemia	130	7 (5.4)	7 (5.4)	1 (0.8)	0	15 (11.5)
Blood bilirubin increased	130	4 (3.1)	3 (2.3)	0	0	7 (5.4)
Hypercalcemia	130	4 (3.1)	0	0	0	4 (3.1)
Hyperkalemia	130	1 (0.8)	0	0	0	1 (0.8)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; Version 4.0; N = number of patients in the population; n = number of patients with graded lab value; N1 = number of patients with a nonmissing baseline result and a nonmissing postbaseline result, and as denominators for the percentages.
Source: smlbmaxgrad.

In line with findings in MONARCH 3 and MONARCH 2.

MONARCH 1

MedDRA Terms	Age <65 N=90 n (%)	Age 65-74 N=32 n (%)	Age 75-84 N=9 n (%)	Age 85+ N=1 n (%)
Total AEs	90 (100.0)	32 (100.0)	9 (100.0)	1 (100.0)
Serious AEs				
Total	21 (23.3)	8 (25.0)	2 (22.2)	1 (100.0)
Fatal	1 (1.1)	1 (3.1)	1 (11.1)	0
Hospitalization/prolong existing hospitalization	20 (22.2)	7 (21.9)	1 (11.1)	1 (100.0)
Life-threatening	3 (3.3)	3 (9.4)	1 (11.1)	0
Disability/incapacity	1 (1.1)	1 (3.1)	0	0
Other (medically significant)	2 (2.2)	2 (6.3)	1 (11.1)	0
AE leading to drop- out[a]	5 (5.6)	4 (12.5)	0	1 (100.0)
Psychiatric disorders[b]	12 (13.3)	7 (21.9)	2 (22.2)	0
Nervous system disorders[b]	38 (42.2)	15 (46.9)	3 (33.3)	0
Accidents and injuries[c]	3 (3.3)	3 (9.4)	0	1 (100.0)
Cardiac disorders[b]	6 (6.7)	2 (6.3)	1 (11.1)	1 (100.0)
Vascular disorders[b]	14 (15.6)	3 (9.4)	1 (11.1)	1 (100.0)
Cerebrovascular disorders[d]	0	0	0	0
Infections and infestations[b]	31 (34.4)	7 (21.9)	2 (22.2)	1 (100.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[e]	12 (13.3)	7 (21.9)	0	1 (100.0)
Other AE appearing more frequently in older patients		See Table 6.5		

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in population; n = number of patients in category; SMQ = standardised MedDRA query.

Discontinuation due to AES

Discontinuations from treatment due to AEs were experienced by 10 patients (7.6%) and included the following (1 patient each): abdominal pain, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhoea, ECG QT prolonged, embolism, fatigue, hip fracture, and lymphopenia.

Adverse Event of Special Interest (AESI)

Neutropenia

Neutropenia is a known adverse drug reaction of CDK 4/6 inhibitors due to their mode of action. It is evident that neutropenia is less of a concern for abemaciclib as compared to palbociclib and ribociclib (81 % [55 % Grad 3] and 74 % [60 % Grad 3/4] respectively). The incidences for abemaciclib treated patients in **M3**, **M2** and **M1** are 43.7 % (22 % Grade 3; 1.8 % Grade 4), 46.0 % (23.6 % Grade 3; 2.9 % Grade 4) and 37.1 % (18.9 % Grade 3; 5.3 % Grade 4) respectively. In terms of laboratory abnormalities, neutrophil count decreased were reported in 80.5 % (20.1 % Grade 3; 2.9 % Grade 4), 87.1 (28.6 % Grade 3; 3.5 % Grade 4) and 87.7 % (22.3 % Grade 3; 4.6 % Grade 4) in **M3**, **M2** and **M1** respectively.

The median time to onset of TEAEs of Grade 3 or 4 neutropenia was similar in all three studies (33, 29 and 29 days in **M3**, **M2** and **M1** respectively). Median time to resolution of Grade ≥3 neutropenia was also similar (11, 15 and 14.5 days in **M3**, **M2** and **M1** respectively).

Neutropenia events leading to treatment discontinuations were in general low (3 %, 10 % and 24 % in the respective studies). The rather few occurrences of febrile neutropenia is also recognized (0.3 %, 1.4 % and one case in **M3**, **M2** and **M1** respectively).

In **M3** 13 % experienced abemaciclib dose reductions and 17 % experienced abemaciclib dose omissions due to TEAEs of neutropenia. About 3 % discontinued any study drug due to AEs of neutropenia (3 patients [0.9%] discontinued all study treatment, and 6 patients [1.8 %] discontinued only abemaciclib).In **M2** the corresponding rates were 10 %, 16 % and about 2 %. In **M1** 11 % experienced dose reductions and 16 % experienced dose omissions due to TEAEs of neutropenia.

Infections

Infections occurring in the abemaciclib treated patients were reported in 45 % (5.5 % Grade 3; 1.5 % Grade 4) and 42.6 (5.0 % Grade 3; 0.7 % Grade 4) in **M3** and **M2** respectively. The most frequently reported were upper respiratory tract infection (~ 11 %), urinary tract infection (9 %), and lung infection (6 %). In the **M1** study infections were observed in 31.1% of the patients.

SAEs were reported for 6.8 %, 5.9% and 4.5% of the patients in **M3**, **2** and **1** respectively and they were fatal for 4 patients in **M3** (lung infections), 3 patients in **M2** (2 sepsis, 1 lung infection) and 2 patients in **M1** (1 sepsis, 1 lung infection). TEAEs due to infections required discontinuation of study drug in 9 patients (2.8 %) in **M3** study (due to lung infections), in 7 (1.6%) patients in **M2**.

In **M3** there were four Grade 5 events of lung infection (two patients had normal neutrophil counts at the time of the event and one had Grade 1 neutrophil count). In **M2** there were four fatalities including three due to sepsis and one case due to lung infection.

The risk of infections including lung-infections associated with abemaciclib therapy is reflected in Section 4.4 of the SmPC. Moreover, although the Applicant stated that a clear relationship between severe neutropenia and concurrent severe infection across studies has not been demonstrated, deaths due to infections/sepsis in the context of neutropenia were reported.

Diarrhoea

Diarrhoea is the predominant ADR associated with abemaciclib. In **M3**, **M2** and **M1** diarrhoea were reported in 82.3 % (9.5 % Grade 3 [no Grade 4]), 86.4 (13.4 % Grade 3 [no Grade 4]) and 90.2 % (19.7 % Grade 3 [no Grade 4]) of the abemaciclib treated patients in the respective studies. In **M3** and **M2** respectively , 13.8 % and 18.8% had dose reductions due diarrhoea whilst in **M1** it was 21 %. Dose omissions were required in 15.3 % and 18.8 % in **M3** and **M2** respectively.

Reassuring is that few patients discontinued due to diarrhoea however the vast need for concomitant anti-diarrheals is recognized. It is also noted that a high proportion of patients continued to report diarrhoea all through subsequent treatment cycles. In **M2**, the median number of days that patients were treated with abemaciclib at 200 mg or 150 mg twice a day prior to discontinuation or dose reduction for any reason (including disease progression) was 34 days and 92 days, respectively. For the overall safety population, the median number of days to the first dose reduction due to diarrhoea was 29 days. The median number of days to the first dose reduction due to diarrhoea was 16.5 days and 38 days for patients treated with abemaciclib at 200 mg or 150 mg twice a day, respectively. The median number of days to the first dose reduction due to any AE was 29 days and 60 days for patients treated with abemaciclib at 200 mg or 150 mg twice a day, respectively.

In **M3**, the median number of days to first dose reduction due to diarrhoea was 37.5 days, consistent with the observations in **M2** for patients receiving a starting dose of 150 mg (38 days).

The SmPC Sections 4.2 and 4.4 adequately reflects information on diarrhoea, including management and dose adjustment.

Further to diarrhoea in terms of GI disorders, **nausea** and **vomiting** were frequently reported (in **M3** 41.3 % and 30.3 % respectively and in **M2** 45.1 % and 25.9 % respectively). In **M1** it was even higher likely due to the higher dose (nausea 64.4, vomiting 34.8 %). Reports for **decreased appetite** are thus not unexpected (26.3 %, 26.5 % and 45.5 % in **M3**, **M2** and **M1** respectively).

Blood creatinine increased

Laboratory abnormalities in terms of blood creatinine increased were commonly reported. In **M3**, **M2** and **M1** the proportions were 98.1 % (2.9 % Grade 3 [no Grade 4]), 98.4 (1.2 % Grade 3 [no Grade 4]) and 98.5 (0.8 % Grade 3 [no Grade 4]) in the abemaciclib treated patients in the respective studies. The Applicant argues that in vitro and clinical data have showed that abemaciclib and its metabolites (M2 and M20) are inhibitors of the renal OCT 2, MATE1, and MATE2-K transporters. A clinical pharmacology study designed to investigate the effects of abemaciclib on renal tubular secretion and on GFR demonstrated that estimated GFR based on cystatin C is more consistent with actual GFR and that abemaciclib had no effect on GFR as measured by iohexol clearance (please refer also to the PK sections).

Although it is recognized that the majority of reports constitutes isolated blood creatinine increases, acute kidney injury (AKI) was reported in about 2.8 % in **M3** and 1.4 % in **M2**. A clear evidence of relationship between study drug and events of AKI is difficult to draw in these patients, due to the presence of confounding factors (e.g. previous or concomitant episodes of diarrhoea, nausea or vomiting, comorbidities or baseline elevated creatinine). A possible relationship cannot however, be completely excluded. The SmPC reflects the risk of dehydration secondary to diarrhoea.

Hepatic events

Alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased are commonly reported. In **M3** and **M2** ALT reports occurred in 53.4 (7.3 % Grade 3, 0.6 % Grade 4) and 41.0 % (3.9 % Grade 3, 0.7 % Grade 4) in the abemaciclib treated patients respectively. For AST it was 44.4 % (5.1 % Grade 3 [no Grade 4]) and 37.4 % (3.9 % Grade 3 [no Grade 4]) in the respective studies. Blood bilirubin increased occurred in a reassuringly low proportion.

In **M3**, reports of patients with ≥ 1 hepatic TEAE was 26.6 % of the abemaciclib treated patients mainly ALT increased 17.4 %, AST increased 16.8 %. Drug induced liver injury (DILI) occurred in two patients (0.5 %). In **M2** it was 19.5 % and similarly mainly ALT increased 13.4 %, AST increased 12.2 %. There were no reports of DILIs. Two patients in **M2** study dead due to hepatic failure and hepatic function abnormal. There were no Hy´s Law cases identified.

Management recommendations and warnings in regard to increased ALT and AST are reflected in in Sections 4.2 and 4.4 of the SmPC

The Applicant proposes to include `Liver injury´ as an important potential risk and a targeted follow-up for any AE of hepatobiliary disorders is included in pharmacovigilance activities in order to further characterize the potential risk of liver injury. This is considered acceptable.

Venous thromboembolic events (VTEs)

In **M3** and **M2** VTEs were reported in 6.1 % (1.5 % Grade 3, 0.6 % Grade 4) and 4.8 % (1.8 % Grade 3, 0.2 % Grade 4) of the abemaciclib treated patients as compared 0.6 % (no Grade 3, 0.6 % Grade 4) and 0.9 % (0.4 % Grade 3 [no Grade 4]) in the respective control arms. Additionally, in **M3** there were three patients (0.9%) with fatal outcome. The increased risk of venous thromboembolic events associated with advanced/ metastatic cancer in general and the risk associated with endocrine treatment is well recognised. The increase observed in the investigational arms compared to the control arm is however of concern and therefore VTE as an adverse drug reaction for abemaciclib is addressed in sections 4.4 and 4.8. VTE is also included in the safety specification in the RMP.

No new concerns or signals have been identified in the requested safety updates of the AESIs (neutropenia, infections, diarrhoea, blood creatinine increased, hepatic events and VTEs). There is no evidence of any cumulative toxicity.

Electrocardiograms

QT prolongation is not considered an AESI of abemaciclib but relevant to comment. Preclinical, clinical pharmacology and clinical data has not revealed any clinically meaningful prolongation of QT/QTc interval by abemaciclib as opposed to, for example, ribociclib.

Immunological events

Not addressed in the dossier and will be not requested.

Safety related to drug-drug interactions and other interactions

Drug-interaction studies were conducted with the CYP3A inhibitor clarithromycin (Study JPBE) in patients and the CYP3A inducer rifampin (Study JPBF) in healthy subjects. Single doses of abemaciclib in both studies were

generally well tolerated and the AE profiles were similar when abemaciclib was administered alone or with the coadministered drug. Abemaciclib should not be coadministered with inducers of CYP3A such as rifampin due to substantial reductions in abemaciclib and active metabolite exposure.

No clinically significant interactions were observed between abemaciclib and loperamide, a P-gp substrate, indicating that loperamide can be safely administered with abemaciclib.

Post-marketing experience

On September 28 2017, abemaciclib in combination with endocrine therapy or as monotherapy, was approved by the FDA. There are no new concerns or signals evoked at this stage based on the post-marketing experience, however, the information is still very limited.

2.10.1. Discussion on clinical safety

The safety database encompasses patients treated with abemaciclib in combination with AI in the **MONARCH 3** (**M3**) study (2:1 design, N=327 and N=161 in the experimental and control arm respectively), in combination with fulvestrant in the **MONARCH 2** (**M2**) study (2:1 design, N=441 and N=223 in the experimental and control arm respectively) and as monotherapy in the **MONARCH 1** (**M1**) study (N**=**132).

The safety profile of abemaciclib regardless of choice of endocrine partner or as monotherapy (the higher dose of 200 mg BID is recognized) as characterized in **M3**, **M2** and **M1** is very inter-study consistent. The vast majority reported ≥ 1 TEAE and a substantial rate of TEAEs ≥ 3 and SAEs were reported in the respective experimental arms. Notwithstanding, the low rate of treatment discontinuations due to TEAEs as reported in each study is considered reassuring. The number of deaths due to AEs does not evoke any concern at this point.

Neutropenia

Neutropenia is a known adverse drug reaction of CDK 4/6 inhibitors due to their mode of action. It is evident that neutropenia is less of a concern for abemaciclib as compared to palbociclib and ribociclib (81 % [55 % Grade 3] and 74 % [60 % Grade 3/4] respectively). The incidences for abemaciclib treated patients in **M3**, **M2** and **M1** are 43.7 % (22 % Grade 3; 1.8 % Grade 4), 46.0 % (23.6 % Grade 3; 2.9 % Grade 4) and 37.1 % (18.9 % Grade 3; 5.3 % Grade 4) respectively. In terms of laboratory abnormalities, neutrophil count decreased were reported in 80.5 % (20.1 % Grade 3; 2.9 % Grade 4), 87.1 (28.6 % Grade 3; 3.5 % Grade 4) and 87.7 % (22.3 % Grade 3; 4.6 % Grade 4) in **M3**, **M2** and **M1** respectively.

Neutropenia events leading to treatment discontinuations were in general low (3 %, 10 % and 24 % in the respective studies). The rather few occurrences of febrile neutropenia is also recognized.

Compared to palbociclib (Ibrance) and ribociclib (Kisqali), abemaciclib conveys a lesser risk of neutropenia, which appears to be well manageable with risk minimization measures as proposed in the SmPC. The Applicant proposed to include `Severe Infections secondary to neutropenia´ in the RMP which is supported.

Infections

Grade ≥3 occurring in the abemaciclib treated patients were reported in about 5.5 % of patients. Frequently reported were upper respiratory tract infection and lung infection. In **M3** there were four Grade 5 events of lung infection (two patients had normal neutrophil counts at the time of the event and one had Grade 1 neutrophil count). In **M2** there were four fatalities including three due to sepsis and one case due to lung infection.

Diarrhoea

Diarrhoea is the predominant ADR associated with abemaciclib. In **M3**, **M2** and **M1** diarrhoea were reported in 82.3 % (9.5 % Grade 3 [no Grade 4]), 86.4 (13.4 % Grade 3 [no Grade 4]) and 90.2 % (19.7 % Grade 3 [no Grade 4]) of the abemaciclib treated patients in the respective studies. Dose reductions due to diarrhoea were required in about 15-20% of the patients. Dose omissions were reported in similar percentages.

Few patients discontinued due to diarrhoea, however the vast need for concomitant anti-diarrheals is recognized. It is also noted that a high proportion of patients continued to report diarrhoea all through subsequent treatment cycles.

Different clinical trials have used different food recommendations and the Applicant states that there is no clear effect of food on the incidence of diarrhoea. A clinical study has however been requested by the FDA to evaluate the incidence of dose adjustments due to diarrhoea when abemaciclib is administered with or without food (estimated completion date December 2021). The Applicant is recommended to submit these results (Study I3Y-MC-JPCP) when available (around December 2021). Further to diarrhoea in terms of GI disorders, **nausea** and **vomiting** were frequently reported about 30 and 40%, respectively, in **M1** at even higher frequencies, likely due to the higher dose.

Blood creatinine increased

Laboratory abnormalities in terms of blood creatinine increased were reported in close to all patients (98%), but Grade 3 in about 1-2% and no grade 4 events.

Abemaciclib and its metabolites (M2 and M20) are inhibitors of the renal OCT 2, MATE1, and MATE2-K transporters and a study designed to investigate the effects of abemaciclib on GFR demonstrated that abemaciclib had no effect on GFR as measured by iohexol clearance (please refer also to the PK sections).

It is recognized that the majority of reports constitutes isolated blood creatinine increases. Acute kidney injury was reported in about 2%, i.e. consistent with GI adverse effects.

Hepatic events

Alanine aminotransferase (ALT) increase and aspartate aminotransferase (AST) increase are commonly reported, about 40-45% overall, Grade 3 about 5% and about 1% Grade 4. Blood bilirubin increased occurred in individual patients.

In **M2,** a total of 19.5 % of the patients reported ≥ 1 hepatic TEAE. The majority was ALT increased (13.4 %). Drug induced injury (DILI) and hepatic failure were reported two (0.5 %) patients each. For contextualization, ribociclib (Kisqali) approved in combination with AI, hepatobiliary toxicity events (including hepatocellular injury, drug-induced liver injury, hepatotoxicity, hepatic failure) occurred in 24.0% with 11.4% grade 3/4 adverse events reported. Increases in transaminases were observed with Grade 3 or 4 increases in ALT (10.2%) and AST (6.9%).

Management recommendations and warnings are reflected in Sections 4.2 and 4.4 of the SmPC for increased ALT and AST. The Applicant proposes to include `Liver injury´ as an important potential risk in the RMP which is supported.

Venous thromboembolic events (VTEs)

VTEs were reported in 5.3 % (1.7 % Grade 3, 0.3 % Grade 4) as compared with <1% overall in the control arms. Additionally, in **M3** there were three patients (0.9%) with a fatal outcome.

Whilst well recognizing the increased risk of venous thromboembolic events associated with advanced/ metastatic cancer in general and the risk associated with endocrine treatment, this increase (including fatal events) in abemaciclib treated patients is of concern. As abemaciclib treatment conveys an increased risk of VTEs this is reflected in Sections 4.4 and 4.8 in addition to be addressed in the RMP.

No new concerns or signals have been identified in the requested safety updates of the AESIs (neutropenia, infections, diarrhoea, blood creatinine increased, hepatic events and VTEs) or in the data from the US post-marketing experience (albeit limited). There is no evidence of any cumulative toxicity.

QT prolongation is not considered an AESI of abemaciclib, as abemaciclib appears not to prolong the QT interval to any clinically relevant extent.

2.10.2. Conclusions on the clinical safety

The safety profiles of the respective abemaciclib combinations as characterized in studies **M3** and **M2** are very similar suggesting that the safety profile of abemaciclib is not anticipated to alter to any major extent regardless of choice of accompanying endocrine therapy. The similarity to that of abemaciclib monotherapy is also recognized.

In contrast to the two currently approved CDK4/6 inhibitors palbociclib (Ibrance) and ribociclib (Kisqali) where neutropenia was the overarching tolerability concern, with abemaciclib it is diarrhoea which requires a multitude of counter-acting measures including frequent dose reductions/omissions in order to be manageable. Neutropenia is much less of a concern. Notwithstanding, given the acceptable low treatment discontinuation rate, the overall abemaciclib toxicity appears to be manageable with appropriate risk minimization measures.

2.11. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	Venous Thromboembolic Events
Important Potential Risks	Serious Infection Secondary to Neutropenia Liver Injury Reproductive and Developmental Toxicity
Missing Information	Exposure and safety in patients with severe renal impairment

Pharmacovigilance plan and Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Venous thromboembolic events	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 • Recommendations for VTE monitoring are included in SmPC Section 4.4 • Reported frequencies for VTE adverse reactions are included in SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Thromboembolism follow-up form **Additional pharmacovigilance activities:** None
Important Potential Risks		
Serious infection secondary to neutropenia	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.8 • Recommendations for management of haematological toxicities including neutropenia are included in SmPC Section 4.2 • Recommendations for monitoring and detecting neutropenia are included in SmPC Section 4.4 • Reported frequencies for neutropenia are included in SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Infections follow-up form **Additional pharmacovigilance activities:** None
Liver injury	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.8 • Recommendations for management of increased ALT and AST are included in SmPC Section 4.2 • Recommendation for monitoring in case of increased aminotransferases are included in SmPC Section 4.4 • Reported frequencies for ALT and AST elevations are included in SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hepatic disorder follow-up form **Additional pharmacovigilance activities:** None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Sections 4.1 and 4.6 • Recommendations for pre-/peri-menopausal women who are administered with abemaciclib in combination with endocrine therapy are included in SmPC Section 4.1 • Recommendation for women of child-bearing potential are included in SmPC Section 4.6	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy and Breast-Feeding Maternal follow-up Form **Additional pharmacovigilance activities:** None
Missing information		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Exposure and safety in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2 • Recommendations and information for administering abemaciclib in patients with severe renal impairment are included in SmPC Sections 4.2 and 5.2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Routine pharmacovigilance activities as well as routine risk minimisation measures are considered sufficient to manage the safety concerns of Verzenios.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.12. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The Applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.09.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.13. New Active Substance

The Applicant compared the structure of abemaciclib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers abemaciclib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.14. Product information

2.14.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.14.2. Labelling exemptions

A request to omit all particulars from the immediate labelling has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons:

The product will be marketed as film-coated tablets supplied in blisters sealed in a wallet card. The company requested to omit printing of the minimum particulars on the blister foil as it will be extremely difficult for the patient to tear the wallet card apart and remove the blister.

The QRD Group rejected the request to omit completely particulars on the blister foil since there is no guarantee that the blister cannot be separated from the wallet. The Group requested to have the minimum particulars to be printed on the blister foil as follows: Invented name, strength, INN, EXP and Lot.

2.14.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Verzenios (abemaciclib) is included in the additional monitoring list as new active substance.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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.

3.1.2. Available therapies and unmet medical need

Breast cancer is estimated to cause about 500 000 deaths worldwide annually, and this is a consequence of the almost invariably fatal advanced disease setting relevant to the sought indication. For ER+, HER2-negative patients, the following treatment options pertain to the respective parts of the proposed indication:

• First line endocrine therapy; aromatase inhibitors (AI), tamoxifen, fulvestrant, AI + CDK4/6 inhibitor, AI + everolimus (conditional on adjuvant AI).

• Second line endocrine therapy; AI, tamoxifen, fulvestrant, fulvestrant + palbociclib, AI + everolimus, and megestrol acetate are options.

3.1.3. Main clinical studies

The two pivotal trials pertain to the respective parts of the proposed indication are:

MONARCH-3: randomized 328:165 patients, double-blind, abemaciclib 150 mg BiD or placebo as add-on to non-steroidal AI in ER+ HER2- breast cancer, 1st line postmenopausal.

MONARCH-2: randomized 446:223 patients, double-blind, abemaciclib 150 mg BiD or placebo add-on to fulvestrant (+GNRH agonist if not postmenopausal) in ER+ HER2- breast cancer with progression on endocrine therapy in the (neo) adjuvant (< 12 months) or metastatic setting.

3.2. Favourable effects

MONARCH-3:

- PFS by investigator (primary endpoint), median 28 vs. 15 months in abemaciclib + NSAI vs. placebo + NSAI, HR 0.54 (p = 0.000002). Event rate 42% vs. 66%.
- ORR, 48% vs. 35%, OR 1.8 (nominal p= 0.002).
- OS, median NR vs. NR, HR 1.1 (p= 0.80). Event rate 19% vs. 18%.

MONARCH-2:

- PFS by investigator (primary endpoint), median 16 vs. 9.3 months in abemaciclib + fulvestrant vs. placebo + fulvestrant, HR 0.55 (p = 0.0000001). Event rate 50% vs. 70%.
- ORR, 35% vs. 16%, OR 2.8 (nominal p< 0.001).
- OS, median NR vs. NR, HR 0.85 (p= 0.39). Event rate 19% vs. 22%.

3.3. Uncertainties and limitations about favourable effects

No major uncertainties remain apart from the immature OS data and the biomarker analysis that the Applicant is recommended to submit.

3.4. Unfavourable effects

The respective safety profiles as characterized in studies **MONARCH 3** (abemaciclib + AI, N=327) and **MONARCH 2** (abemaciclib + fulvestrant, N=441) seems overall fairly consistent.

Overall there is quite a substantial difference most and foremost in the proportion of patients experiencing Grade ≥3 AEs (58-68% of patients across studies) but also SAEs between the abemaciclib containing arms and the control with the majority considered treatment related. This however, does not translate into a corresponding magnitude regarding treatment discontinuations in either study and the number of deaths due to AEs does not evoke any immediate concerns at this point. Altogether, this may point to a manageable safety profile but not without appropriate risk minimization measures as nearly half of the patients across studies experienced a dose reduction due to AEs (mostly due to diarrhoea and neutropenia).

Diarrhoea is the predominant abemaciclib ADR (reported by > 80 % across studies). Judging however by the fairly low proportion of abemaciclib treated patients that discontinued due to diarrhoea, this appears manageable albeit not without the requirement of appropriate measures like anti-diarrheals and dose adjustments. A high need of concomitant medications for the management of diarrhoea is evident including in patients with Grade 1 or Grade 2 events. It is further noted that a high proportion of patients continue to report events of diarrhoea all through the treatment cycles.

Neutropenia is much less reported than with Ibrance and Kisqali and appears manageable considering the low proportion of treatment discontinuations and rather few events of febrile neutropenia/ neutropenic sepsis/ neutropenic infection. A decrease in neutrophil counts is generally observed at Cycle 2 and maintained over the course of treatment.

Other commonly reported TEAEs in the abemaciclib containing arms include fatigue, nausea, abdominal pain, anaemia, vomiting and alopecia.

Creatinine increase was reported in approximately 98% of the patients and occurred within the first cycle of abemaciclib dosing, remained elevated but stable through the treatment period and reversible upon treatment discontinuation. Abemaciclib and its metabolites (M2 and M20) are inhibitors of the renal OCT 2, MATE1, and MATE2-K transporters and a study designed to investigate the effects of abemaciclib on GFR demonstrated that abemaciclib had no effect on GFR as measured by iohexol clearance (please refer also to the PK sections).

In terms of VTE events, there is an increase in reports (including fatal events) for the abemaciclib treated patients without any obvious difference in risk factors between the experimental arms and the control arms. The risk of VTE is reflected in the SmPC.

Safety updates of AESIs (neutropenia, infections, diarrhoea, blood creatinine increased, hepatic events and VTEs) including discontinuations due to AEs and permanent dose reductions for patients treated for < 12 months, 12 to 18 months and > 18 months for the experimental and control arms, have been provided. For all AESIs the highest rate of TEAEs, severity (≥3) and the need for dose reductions occurred during the time period of 0-12 months which is likely to be indicative of adequate risk minimisation measures as proposed in section 4.2. The discontinuation rate remains low over time of exposure.

3.5. Uncertainties and limitations about unfavourable effects

Different clinical trials have used different food recommendations and the Applicant states that there is no clear effect of food on the incidence of diarrhoea. A clinical study has however been requested by the FDA to evaluate the incidence of dose adjustments due to diarrhoea when abemaciclib is administered with or without food. The

Applicant is recommended to submit these results (Study I3Y-MC-JPCP) when available (around December 2021).

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
MONARCH-3 (I3Y-MC-JPBM) **Treatment: abemaciclib + non-steroidal aromatase inhibitor** **Control: placebo + non-steroidal aromatase inhibitor**					
PFS	Progression-free survival by investigator	Months	28	15	HR 0.54; 95% CI: 0.42-0.70 p=0.000002 Event rate 42% vs. 66%. Supported in independent review and sensitivity analyses; PFS2.
OS	Overall survival	Months	Median not reached	Median not reached	HR 1.1; 95% CI: 0.68-1.6 p= 0.80 Event rate 19% vs. 18%.
MONARCH-2 (I3Y-MC-JPBL) **Treatment: abemaciclib + fulvestrant** **Control: placebo + fulvestrant**					
PFS	Progression-free survival by investigator	Months	16	9.3	HR 0.55; 95% CI: 0.45-0.68. p=0.0000001 Supported in independent review and sensitivity analyses; PFS2. Event rate 50% vs. 70%.
OS	Overall survival	Months	Median not reached	Median not reached	HR 0.85; 95% CI: 0.60-1.2. p= 0.39 Event rate 19% vs. 22%.
Unfavourable Effects					

MONARCH 3		**abemaciclib + AI N=327**	**Placebo + AI N=161**	Duration of therapy similar between the two arms: approximately 16 months	
≥ 1 TEAE	%				
- Grade 3		48.6	19.9		
- Grade 4		6.4	1.9		
Diarrhoea	%				
- Grade 3		9.5	1.2		
Neutropenia	%				
- Grade 3		19.6	0.6		
- Grade 4		1.5	0.6		
Fatigue	%				
- Grade 3		1.8	0		
Nausea	%				
- Grade 3		0.9	1.2		

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	
Anaemia		%				
-	Grade 3		5.8	1.2		
MONARCH 2			**abemaciclib + fulvestrant N=441**	**Placebo + fulvestrant N=223**	Duration of treatment: 13 months vs. 9 months exp and control respectively	
≥ 1 TEAE		%				
-	Grade3		54.6	20.6		
-	Grade 4		5.9	2.2		
Diarrhoea		%				
-	Grade 3		13.4	0.4		
Neutropenia		%				
-	Grade 3		23.6	1.3		
-	Grade 4		2.9	0.4		
Nausea		%				
-	Grade 3		2.7	0.9		
Fatigue		%				
-	Any		39.9	26.9		
-	Grade 3		2.7	0.4		
Anaemia		%				
-	Any		29.0	3.6		
-	Grade 3		7.0	0.9		
-	Grade 4		0.2	0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The PFS gain in first advanced line use of abemacilib as add on to a non-steroidal AI compared to NSAI alone, and in the 2nd line population assessed in the fulvestrant add-on study, is comparable to results for approved CDK4/6 inhibitors and is considered a clinically meaningful benefit.

The safety profiles of the respective abemaciclib combinations as characterized in studies **MONARCH 3** and **MONARCH 2** is very similar suggesting that the safety profile of abemaciclib is not anticipated to alter to any major extent regardless of choice of accompanying endocrine therapy. Diarrhoea requiring a multitude of counter-acting measures including frequent dose reductions/omissions in order to be manageable, is the overarching tolerability concern. No new concerns or signals have been identified in the requested safety updates or in the data from the US post-marketing experience (albeit limited). There is no evidence of any cumulative toxicity. It is concluded that the overall abemaciclib toxicity profile with appropriate risk minimization measures as reflected in the SmPC, appears to be manageable as evidenced by the low treatment discontinuation rate which remains low also over time of exposure.

3.7.2. Balance of benefits and risks

The CHMP concludes that the magnitude of the treatment effect on progression-free survival and the manageable toxicity contribute to a positive B/R balance.

3.7.3. Additional considerations on the benefit-risk balance

For the indication abemaciclib + fulvestrant as initial endocrine therapy, the available evidence is limited, though the indication for first-line use can be supported by extrapolation from the demonstrated add-on effect to fulvestrant in the second line, in combination with evidence of efficacy in the first line in combination with AI. The extrapolation to AI + LHRH in premenopausal women can be accepted. Efficacy has been shown for abemaciclib in combination with AI in postmenopausal patients, and in combination with fulvestrant + LHRH in pre/perimenopausal patients, supporting the extrapolation. Furthermore, AI + LHRH constitutes an accepted alternative (to antioestrogens/SERMs) in premenopausal patients, including as first line therapy, according to current clinical practice and European and international therapy guidelines. Effective inhibition of ER signalling is achieved with AI or fulvestrant (+LHRH) alike, as this is the basis for anti-tumour activity of these compounds. This further supports that abemaciclib can be used as add-on, not only to fulvestrant +LHRH, but also to AI +LHRH.

The ORR seen in the single arm MONARCH-1 trial undertaken in a chemotherapy-experienced metastatic breast cancer population is not outstanding and clinical benefit has not been shown. The Applicant revised the indication to remove the monotherapy.

3.8. Conclusions

The overall B/R of Verzenios is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Verzenios is favourable in the following indication:

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 luteinising hormone-releasing hormone (LHRH) agonist.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The 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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that abemaciclib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.