EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 May 2020
EMA/CHMP/321881/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Piqray

International non-proprietary name: alpelisib

Procedure No. EMEA/H/C/004804/0000

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
AESI	Adverse event of special interest
AI	Aromatase inhibitor
ARA	Acid reducing agent
AUC	Area under the plasma or serum concentration-time curve
BCRP	Breast cancer resistance protein
BIRC	Blinded independent review committee
CBR	Clinical benefit rate
CDK4/6	Cyclin-dependent kinase 4/6
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMA	Critical Material Attribute
Cmax	Peak concentration
CPP	Critical process parameter
CTAB	Cetyltrimethylammonium bromide
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
CYP2B6	Cytochrome P450 2B6
CYP2C9	Cytochrome P450 2C9
DCR	Disease control rate
DeO	Design of experiments
DHMA	Danish Health and Medicines Authority
DMC	Data Monitoring Committee
DoR	Duration of response
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EM	Erythema multiforme
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen receptor
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GC	Gas chromatography
GI	Gastrointestinal
HbA1c	Hemoglobin A1c
HER2	Human epidermal growth factor receptor-2
HPLC	High performance liquid chromatography
HR	Hazard ratio
HR-positive	Hormone receptor-positive
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control

IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOD	Limit of detection
LOQ	Limit of quantification
MAH	Marketing Authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NA	Not applicable
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
NCI	National Cancer Institute
NSAI	Non-steroidal aromatase inhibitor
ORR	Overall response rate
OS	Overall survival
PAR	Proven aceptable range
PCTFE	Polychlorotrifluoroethylene
PDE	Permitted daily exposure
Ph.Eur.	European Pharmacopeia
PBPK	Physiologically based PK
PD	Pharmacodynamics
PFS	Progression-free survival
PFS2	Progression-free survival after next line of treatment
PIK3CA	Gene which encodes the p110-α catalytic subunit of PI3K
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetics
PoC	Proof-of-concept
PRO	Patient-reported outcome
PVC	Polyvinyl chloride
QLQ-C30	Quality of life questionnaire – core 30
QbD	Quality by design
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative humidity
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TDD	Time to definitive deterioration
TTP	Time to progression
TTR	Time to response
TYMC	Total Combined Yeasts/Moulds Count
USP/NF	United States Pharmacopoeia / National Formulary
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 19 December 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Piqray, through the centralised procedure falling within the Article 3(1) and point 3 of Annex I to Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017.

The applicant applied for the following indication: Piqray is indicated in postmenopausal women, and men, with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine based regimen.

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) P/0079/2017 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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 alpelisib 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 on the development relevant to the present application on 23 October 2014 (EMEA/H/SA/2907/1/2014/I), 26 January 2017 (EMEA/H/SA/2907/1/FU/1/2016/I), 14 December 2017 (EMEA/H/SA/2907/2/2017/II and EMEA/H/SA/2907/1/FU/2/2017/I) and 19 April 2018 (EMEA/H/SA/2907/2/2017/II).

The scientific advice pertained to the following quality and clinical aspects:

- The advice related primarily to the quality development of the product. In particular, the issues discussed were related to starting materials, demonstration of comparability of the drug substance quality in the MAA and the appropriateness of the demonstration of comparability

between drug products supplied to pivotal trials and proposed commercial supply.

- In addition, one clinical question related to the appropriateness of a bio-waiver request for the proposed commercial formulation regarding one strength was discussed.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Sinan B. Sarac

The application was received by the EMA on	19 December 2018
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	29 May 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 July 2019
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at four clinical investigator sites in Chile, Peru and Japan and at the Laboratory in US between 14 May 2019 and 25 September 2019. The outcome of the inspection carried out was issued on.	14 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	5 September 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 February 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 February 2020

The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	31 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 April 2020
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 April 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	29 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the outstanding issues following oral explanation to all CHMP members on	14 May 2020
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	15 April 2020
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 Piqray on	28 May 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication is for the treatment of patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine based regimen.

2.1.2. Epidemiology

Breast cancer (BC) is the most common female cancer in Europe with an estimated incidence of over half a million women in 2018 (Ferlay, 2018). It is also the second leading cause of cancer-related death (National Breast Cancer Foundation 2018). That represents twice as many new BC cases annually than those of cancer in any other site and one case out of every eight European women before they reach the age of 85. Around 80% of the BC cases in Europe will appear in women over 50 years.

In men, breast cancer is a rare condition constituting < 1% of all breast cancer diagnoses (Siegel et al 2018).

2.1.3. Biologic features

Breast cancer can be categorised into different histopathologic subtypes based on the expression of the oestrogen receptor (ER), the progesterone receptor (PR), and HER2 receptor overexpression or gene amplification. The predominant subset of breast cancer is HR-positive, HER2-negative disease. Of the new cancers diagnosed worldwide each year, approximately 60%-65% are HR-positive, 20%-25% are HER2-positive, and 15%-18% are triple negative (Finn et al 2015).

The cyclinD-CDK4/6-pRB axis has been described as relevant in HR-positive Breast cancer (Lamb et al 2013). Signalling through the PI3K/Akt/mTOR pathway also appears relevant in HR+ HER2- breast cancer. The PI3K pathway is a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival, and apoptosis. Constitutive activation of PI3K signalling is known to be a critical step in mediating the transforming potential of oncogenes and tumour suppressors in many tumour types, with PI3K as the oncogenic driver of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway (Liu et al 2009). Aberrant induction of PI3K pathway activity can occur through several events including upstream genetic alterations in receptor tyrosine kinases (RTKs), loss-of-function mutations in the tumour suppressor genes (such as PTEN) as well as mutations in PIK3CA, the gene encoding PI3Kα (Rodon et al 2013).

PIK3CA mutations are reported in 36% of all breast cancers and in up to 45% of HR-positive, HER2-negative tumours (Table 1).

Table 1: PIK3K signalling pathway mutations and alterations in breast cancer

	PIK3CA mutation	PTEN mutation/loss
All breast tumors	36%	NR
HR-positive, HER2-negative	45%	13%
HER2-positive	39%	4%
Triple negative	9%	35%

HER2 human epidermal growth factor receptor-2, HR hormone receptor, NR not reported, PI3K phosphatidylinositol-3-kinase

Source: The Cancer Genome Atlas Network 2012

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging and confirmed by pathological assessment. Disease stage is assessed according to the TNM system. Prognostic and predictive factors for breast cancer include hormone receptor and HER2 expression.

The targeted population is advanced HR positive, HER-2 negative breast cancer patients with a PIK3CA mutation. Despite hormone-sensitive tumours have better prognosis than other subtypes they are still responsible for most of the BC-related deaths due to their high prevalence, comprising 60%-65% of all cases. The median OS is approximately 42 months in this patient population (Gobbini EJC 2018).

The presence of PIK3CA mutations was reported to be an independent negative prognostic factor in a pooled analysis of nearly two thousand ABC patients (Sobhani et al 2018).

2.1.5. Management

Chemotherapy and endocrine therapy form the backbone of the palliative systemic treatment of advanced breast cancer (ABC), including hormone-positive breast cancer. Treatment is case-tailored based on tumour and patient characteristics and the treatment choice has historically been based on the perceived aggressiveness of the disease.

Endocrine therapy is the treatment of choice for patients with HR-positive advanced breast cancer. Endocrine therapies include selective ER modulators (e.g. tamoxifen), selective nonsteroidal aromatase inhibitors (NSAI; e.g. letrozole and anastrozole), steroidal AIs (e.g. exemestane), and ER antagonists (e.g. fulvestrant) (Cardoso et al 2018). In contrast to women, male patients with HR-positive, HER2-negative breast cancer have few approved treatment options due to sex-based differences in estrogen production and thus their endocrine-based therapeutic options are limited, although in practice female breast cancer treatment guidelines are also followed (Giordano et al 2002, Agrawal et al 2007, Patten et al 2013, Foerster et al 2014).

Endocrine therapy (ET) may be given in first, second, or later lines of therapy for advanced breast cancer (NCCN 2018, ESMO 2018). Progressive disease ultimately develops in all patients, either due to primary resistance (de novo resistance defined as progressive disease (PD) within the first 6 months of first line ET for ABC, while on ET) or relapse/progression following an initial response (acquired resistance defined as PD ≥ 6 months after initiating ET for ABC, while on ET) (ESMO 2018). Despite significant advances in treating patients with HR-positive breast cancer, the development of endocrine resistance and hence disease progression remains a critical problem (Shah and Dickler 2014).

Once ABC progresses after first line endocrine therapy, treatment options include switching to another not previously used endocrine-based treatment, proceeding to chemotherapy or to one of the novel targeted therapy-based combinations. Chemotherapy is usually preferred in cases of visceral involvement or when the disease is perceived to be advancing at a fast pace (ESMO 2018).

Two classes of targeted compounds (mTOR inhibitors, e.g. everolimus, and cyclin dependent kinase 4/6 (CDK4/6) inhibitors, e.g. palbociclib, ribociclib, and abemaciclib) have demonstrated clinical efficacy when combined with endocrine therapy and obtained regulatory approvals in advanced HR-positive, HER2-negative breast cancer (EPAR Ibrance, EPAR Verzenios, EPAR Afinitor, EPAR Kisqali).

Currently available treatment options for HR-positive, HER2-negative advanced breast cancer with details on the magnitude of their treatment effect and important safety and tolerability issues are summarised in Table 2.

Table 2: Summary of available targeted therapies for HR-positive, HER2-negative advanced breast cancer

Relevant indication (treatment of HR-positive, HER2-negative advanced breast cancer)	Basis for approval	Important safety and tolerability issues (most common ADRs at an incidence ≥ 20%)
mTOR inhibitor		
Everolimus (10 mg daily) plus exemestane (25 mg daily)		
In combination with exemestane in postmenopausal women with disease progression following NSAI therapy	vs. exemestane PFS 7.8 vs. 3.2 months (HR = 0.45; p < 0.0001); BOLERO-2	Stomatitis, infections, rash, fatigue, nausea, diarrhea, weight decreased, decreased appetite, arthralgia, dysgeusia, headache, cough, and dyspnea
Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors		
Abemaciclib (150 mg twice daily)		
In combination with fulvestrant in women with disease progression following endocrine therapy	vs. fulvestrant PFS 16.4 vs 9.3 months (HR = 0.55; p < 0.001); MONARCH-2	Diarrhea, neutropenia, nausea and fatigue, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache
As monotherapy in subjects with disease progression following endocrine therapy and prior chemotherapy (1-2 regimens) in the metastatic setting	Abemaciclib PFS 6.0 months MONARCH-1	Diarrhea, fatigue, nausea, decreased appetite, abdominal pain, vomiting, headache, increased creatinine, neutropenia, leukopenia, anemia, platelet count decreased, ALT/ALP increase, hypokalemia, and hyponatremia
Palbociclib (125 mg daily) plus fulvestrant (500 mg)		
In combination with fulvestrant in women with disease progression following endocrine therapy	vs. fulvestrant PFS 9.5 vs. 4.6 months (HR = 0.46; p < 0.0001); PALOMA-3	Infections, neutropenia, leukopenia, anemia, thrombocytopenia, headache, fatigue, nausea, stomatitis, diarrhea, and constipation
Ribociclib (600 mg daily) plus fulvestrant (500 mg)		
In combination with fulvestrant in postmenopausal women either as initial endocrine-based therapy or with disease progression following	vs. fulvestrant PFS 20.5 vs. 12.8 months (HR = 0.59; p = 4.10×10^{-7}); MONALEESA-3	Neutropenia, nausea, fatigue, diarrhea, leukopenia, vomiting, constipation, arthralgia, cough, and headache

ADR adverse drug reaction, ALP alkaline phosphatase, ALT alanine aminotransferase, HER2 human epidermal growth factor receptor-2, HR hazard ratio, HR-positive hormone receptor-positive, mTOR mammalian target of rapamycin, NSAI non-steroidal aromatase inhibitor, PFS progression-free survival,

Source: drugs@fda, Hortobagyi et al 2016b, Dickler et al 2017, Loibl et al 2017, Sledge et al 2017, and Slamon et al 2018

About the product

Alpelisib is an α specific class I phosphatidylinositol3kinase (PI3Kα) inhibitor. Phosphatidylinositol-3-kinases (PI3Ks) are a family of lipid kinases that are important in controlling signalling pathways involved in cell proliferation, motility, apoptosis and cell invasion as well as glucose metabolism. Gain of function mutations in the gene encoding the catalytic α subunit of PI3K (PIK3CA) lead to activation of PI3Kα and AKT signalling, cellular transformation and the generation of tumours in *in vitro* and *in vivo* models.

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets including AKT, and showed activity in cell lines harbouring a PIK3CA mutation.

In vivo, alpelisib inhibited the PI3K/AKT signalling pathway and reduced tumour growth in xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in oestrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased anti-tumour activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.

The PI3K/AKT signalling pathway is responsible for glucose homeostasis, and hyperglycaemia is an expected on-target adverse reaction of PI3K inhibition (see SmPC section 5.1 and pharmacodynamics section of this report).

The recommended indication for Piqray (alpelisib) is as follows:

Piqray is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

Treatment with Piqray should be initiated by a physician experienced in the use of anticancer therapies.

Patients with HR positive, HER2 negative advanced breast cancer should be selected for treatment with Piqray based on the presence of a PIK3CA mutation in tumour or plasma specimens, using a validated test. If a mutation is not detected in a plasma specimen, tumour tissue should be tested if available (see SmPC section 4.2).

The recommended dose is 300 mg alpelisib (2x 150 mg film-coated tablets) taken once daily on a continuous basis. Piqray should be taken immediately after food, at approximately the same time each day (see SmPC section 4.2). The maximum recommended daily dose of Piqray is 300 mg

Piqray should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Dose modifications may be necessary to improve tolerability (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 50, 150 or 200 mg of alpelisib as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, D-mannitol, sodium starch glycolate, Hypromellose and magnesium stearate.

Film coating: Hypromellose, iron oxide black, iron oxide red, macrogol, talc and titanium dioxide.

The product is available in PVC/PCTFE/alu blister packs as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of alpelisib is (2*S*)-*N*1-{4-methyl-5-[2-(1,1,1-trifluoro-2- methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl}pyrrolidine-1,2-dicarboxamide corresponding to the molecular formula $C_{19}H_{22}F_3N_5O_2S$. It has a relative molecular mass of 441.47 g/mol and the following structure:

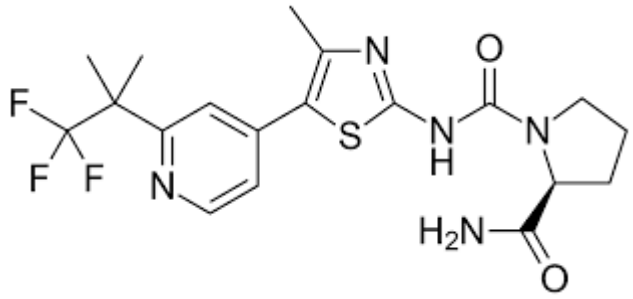


Figure 1: active substance structure

The chemical structure of alpelisib is inferred from the route of synthesis, including the structures and conformation of raw materials and was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, high resolution mass spectrometry, infrared spectroscopy, UV spectroscopy and x-ray crystallography. The solid-state properties of the active substance were investigated by a combination of dynamic vapour sorption, thermogravimetric analysis and x-ray powder diffraction. A single anhydrous polymorph (form A) has been identified.

The active substance is a slightly hygroscopic white crystalline powder. It exhibits pH-dependent solubility, being a weak base and is practically insoluble in aqueous media above pH 2 and slightly soluble in pH 1 hydrochloric acid.

Alpelisib exhibits stereoisomerism due to the presence of a single chiral centre which originates in a starting material.

Manufacture, characterisation and process controls

Alpelisib is synthesized using well defined starting materials with acceptable specifications. There is a single isolated intermediate. The starting materials were the subject of a scientific advice procedure and the applicant followed the advice to include additional steps.

The process is convergent. The originally submitted process description was missing details on amounts of reagents and catalysts, reaction conditions and criticality of steps. Several mutagenic impurities or reagents had been identified and it was proposed to control these according to ICH M7 option 4, i.e. detailed understanding of the process, but the control strategy to implement such an approach was deemed insufficient, resulting in a major objection. The applicant was able to provide a much more detailed process description, as well as extensive details on impurity fate and purge studies which demonstrated an adequate control strategy for control of impurities.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials 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. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced to optimise the process and ensure the quality of the active substance have been presented in sufficient detail and have been justified. The same polymorphic form of active substance has been used throughout development and clinical studies.

The active substance is packaged in double LDPE bags stored in a drum. The primary packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, particle size distribution (laser diffraction, identity (IR, XRPD), assay (HPLC), impurities (HPLC), enantiomer (chiral HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), and microbial enumeration (Ph. Eur.).

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.

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 assay and impurities testing has been presented.

Analysis data on four production scale batches of the active substance from the proposed commercial manufacturer using the commercial process was provided. The results are within the specifications and consistent from batch to batch. In addition, supportive data from 51 batches manufactured throughout development activities by previous manufacturers using earlier process was provided.

Stability

Stability data from six pilot scale batches of active substance from a manufacturing site different to the planned commercial site, but using the same process, stored in the intended commercial package for up to 24 months under long term conditions (25ºC / 60% RH and 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines was provided. The following parameters were tested: appearance, identity, impurities, enantiomer, water content, clarity and colour of solution, assay, particle size distribution and microbial enumeration. The analytical methods used were the same as for release, (other than the clarity and colour of solution tests which are generally not applied to active substances used in solid oral dosage formulations) and are stability indicating. No significant trends were observed for any of the measured attributes under any storage

conditions, other than a very slight colour change in solution for later timepoints. In addition, testing results for up to 12 months under long term conditions from full production scale batches from the planned commercial site were provided, which show equivalent behaviour to the pilot scale batches.

Photostability testing following the ICH guideline Q1B was performed on one pilot scale batch. A change in colour was observed, as well as an increase in impurities. Therefore, alpelisib is considered photolabile and should be stored protected from light.

Samples were stored under stressed conditions including an open dish study with high temperature and humidity, and forced degradation studies were conducted in water, aqueous acid, base and peroxide. Alpelisib is stable in the solid state, but degrades under acidic, basic and oxidative aqueous conditions.

A freeze/thaw study was also conducted over 1 month without impact on any of the measured parameters.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months below 30°C, protected from light, in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is an immediate release film-coated tablet in three strengths: 50, 150 and 200 mg. The 50 mg tablets are light pink and round, imprinted with L7. The 150 mg tablets are pale red and ovaloid, imprinted with UL7. The 200 tablets are light red and ovaloid, imprinted with YL7.

lpelisib is highly permeable but poorly soluble in aqueous media above pH 2 and is thus considered a BCS class 2 compound. The polymorphic form of the active substance is retained during formulation steps including compression, grinding and granulation.

All excipients, with the exception of the iron oxide colorants, which are commonly used in solid oral dosage forms, are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The compatibility of the active substance with the excipients was demonstrated in dedicated stability studies and the function and content of each was adequately justified. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Various formulations were used throughout clinical trials, with some excipients being changed and the contents and grades of others being modified. It was demonstrated that the proposed commercial tablets are bioequivalent to those used in the pivotal phase 3 study by combination of a clinical bioequivalence study and comparative *in vitro* dissolution profiles. This data was provided during the procedure to resolve a major objection.

Discriminatory power of the dissolution method was investigated using batches manufactured with slightly modified process parameters compared to the commercial finished product. The proposed release method is deemed to be sufficiently discriminatory.

The manufacturing process consists of combining the drug substance and excipients via blending, compression, film-coating, and packaging. The development approach used some tools and concepts from the Quality by Design (QbD) paradigm. Risk assessment was used to identify potentially critical process parameters (CPPs) in the process and these were investigated experimentally. This allowed suitable target set-points and operating ranges to be defined for the CPPs.

The primary packaging is PVC/PCTFE/alu blisters. The materials comply 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 four main steps: blending; compression; film-coating; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on one batch of each strength which demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. A validation scheme was provided for validation studies on a further batch of each strength prior to commercialization. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. CPPs have been identified and suitable controls are in place. Proven acceptable ranges have been defined for relevant parameters in these steps. The available development data, the proposed control strategy and batch analysis data from commercial scale batches manufactured so far fully support the proposed PARs.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, mean mass, identity (UV, HPLC), water content (KF), dissolution (UV), uniformity of dosage units (Ph. Eur.), degradation products (HPLC), assay (HPLC) and microbial enumeration.

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 assay and impurities testing has been presented.

Parameters included in the specification cover all the critical aspects for ensuring the quality of the drug product and guaranteeing safety and efficacy.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk of elemental impurities was deemed negligible which was confirmed by batch analysis data from active substance, excipients, coating pre-mixes and from 3 batches of finished product using a validated ICP-MS method. Each relevant elemental impurity was well below its respective oral PDE. Therefore, no test for elemental impurities is warranted.

A risk evaluation for the possible presence of nitrosamine impurities in the active substance and finished product was conducted in line with the guidance provided in the Question and answers on "Information on nitrosamines for MAHs (EMA/CHMP/428592/2019 Rev. 2).

The assessment covered the synthetic process to the active substance, including raw materials, and the various components of the finished product, as well as its manufacturing process and packaging. No controls are deemed necessary.

Batch analysis results are provided for 3 registration batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional finished product release testing.

Stability of the product

Stability data from three production scale batches of each strength of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH and 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for identity, appearance, degradation products, assay, water content, dissolution, microbial enumeration and crushing strength. The analytical procedures used are stability indicating.

There are no significant changes to impurities or assay under any of the tested conditions, other than a slight increase in one impurity at 30 and 40ºC (well within the specified limit). There was a small increase in water content at 30 and 40ºC but this did not impact on dissolution rate. Overall, the observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive.

A freeze and thaw cycle test was conducted on one batch of each strength. There was no impact on any of the tested properties. In addition, samples of each strength previously stored in the blister packs for up to 9 months were removed from their packaging and placed in an open petri dish (25ºC / 60% RH and 30ºC / 75% RH) for up to 3 months. Other than an increase in water content, there was no impact on measured physical or chemical properties.

Based on available stability data, the proposed shelf-life of 36 months and without special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetable origin.

2.2.4. 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. 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. The major objections raised during the procedure on the lack of detail on the process description and control strategy, and the lack of a bioequivalence study for the 150 mg tablet were adequately resolved.

2.2.5. 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.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

All non-clinical studies relevant for the non-clinical safety assessment of alpelisib (safety pharmacology studies to assess neuronal and respiratory function in rats, pivotal repeat-dose toxicity studies, genotoxicity studies, embryo-foetal development in rats, local tolerance, primary skin irritation/corrosion, *in vitro* phototoxicity and *in vivo* cardiovascular safety pharmacology studies) were conducted in compliance with Good Laboratory Practice (GLP) principles.

A limited number of studies that were mainly investigational (Glucose and insulin tolerance test in C57BL/6 mice and 4-week oral investigative skin toxicity study in female Brown Norway rats) used for dose range finding purposes or as early screens were not conducted under GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro activity

The kinase selectivity profile of alpelisib was examined in biochemical and cellular assays. In biochemical assays, alpelisib inhibited p110α and its most common somatic mutations H1047R, E545K (IC_{50}=4.6 nM, 4.8 nM and 4 nM) more potently than the p110δ (IC_{50}=290 nM), p110γ (IC_{50}=250 nM) and p110β isoforms (IC_{50}=1,156 nM). Alpelisib was also found to lacked activity against the class III family member Vps34, the PIKKs mTOR, DNA-PK and ATR (IC_{50}>9100 nM), other 38 tyrosine and 27 serine/threonine-specific kinases (IC_{50}>10μM) and was significantly less potent against the distinct lipid kinase PIK4β (IC_{50}=581 nM) and cABL (IC_{50}=2000 nM).

Mechanistic cell-based assays confirmed the specificity of alpelisib on Class Ia PI3K isoforms. Alpelisib potently inhibited the phosphorylation of AKT (IC_{50}=74 nM) in Rat1-myr-p110α cells and the phosphorylation of various AKT downstream effectors (direct: pGSK3 beta (S9P); indirect: p70S6K (T389) through mTOR) in two p110α-dependent cell lines, either the mechanistic Rat1-myr-p110α cells, or the MCF7 cells which carry one activating *PIK3CA* mutation (E545K). The inhibition of AKT phosphorylation in Rat1-myr-p110α cells was reversed after 30 minutes suggesting that sustained inhibition of the pathway and downstream effectors would require sufficient and prolonged exposure to the compound. On the contrary, alpelisib showed significant reduced inhibitory activity in the p110β and p110δ isoforms (IC_{50}=2249 and 1213 nM, respectively) measured by quantification of S473P-AKT levels in Rat1-myr-p110 β and δ cells. Furthermore, alpelisib did not reduced RPS6 phosphorylation in TSC1-null MEFs cells, in which rapamycin-sensitive functions of mTORC1 are activated independently of PKB/AKT, supporting that alpelisib does not inhibit mTORC1 and alpelisib did not inhibit ATM or p53 (a downstream effector of PIKKs DNAPK, ATM and ATR) phosphorylation.

In biochemical assays, BZG791, the primary circulating metabolite of alpelisib, was over 500-fold less potent than alpelisib on p110α (IC_{50} = 2343 nM), over 4-fold less potent than alpelisib on the other class I PI3K lipid kinases and, similar to alpelisib, BZG791 was not active on Vps34 and mTOR. Mechanistic cell-based assays confirmed BZG791 shows no activity on the p110α, p110β and p110δ isoforms (IC_{50} >10,000 nM).

Cell proliferation studies in more than 474 cancer cell lines indicated that the foremost positive predictor of alpelisib sensitivity was PIK3CA mutation as well as additional positive and negative associations such as PIK3CA amplification and PTEN mutation, respectively. Alpelisib showed markedly selective activity in PIK3CA mutated cell lines when compared to wild-type cell lines, and when compared to pan-PI3K inhibitors. In addition, alpelisib responsive-cell lines were found to be enriched

in indications such as breast cancer. Among 41 breast cancer cell lines studied in a different assay, HER2 amplified and PIK3CA mutated cell lines were more sensitive to alpelisib.

In vivo activity

Alpelisib PK/PD relationship and *in vivo* anti-tumour activity in mice

To examine the ability of alpelisib to inhibit the PI3K/Akt pathway in a PI3Kα- dependent *in vivo* model, its PK/PD relationship was assessed in a Rat1-myr-p110α tumour bearing mouse model. Each female athymic mouse received a single dose or repeated doses of alpelisib (12.5 mg/kg, 25 mg/kg or 50 mg/kg, p.o). Plasma and tumours samples were collected for PK and PD analysis at different time points. In these experiments, alpelisib treatment was associated with dose and time-dependent inhibition of the PI3K/Akt pathway and near complete inhibition of S473P-Akt for 16 hours, which notably paralleled time-dependent drug exposure in tumour and plasma.

To determine whether dose- and time-dependent pathway inhibition was linked to anti-tumour activity, Rat1-myr-p110α tumour-bearing nude mice were treated orally once a day (qd) with the compound for up to 8 consecutive days. Treatments of 12.5, 25 and 50 mg/kg were well tolerated and resulted in a dose-dependent and statistically significant anti-tumour effect with a T/C of 14.1% and regressions of 9.6 and 65.2% respectively.

To better understand the degree of PI3Kα inhibition that is required for anti-tumour efficacy, the tumour drug concentrations giving 50% (*in vivo* IC50) and 80% (*in vivo* IC80) S473P-Akt inhibition (0.4 and 4 µmol/L, respectively) were first determined by measuring the extent of Akt phosphorylation using RPPA and the specific tumour drug concentration in matched samples from multiple animals and at multiple time points (Figure 13). A nearly linear relationship was found between the anti-tumour efficacy magnitude and duration of drug exposure over the IC80 ($R2=0.80$, $p<0.001$, $n=11$). From this relationship, it appears that 80% inhibition of Akt phosphorylation for at least 29% of the dosing interval is required for alpelisib to induce tumour stasis, and that this level of pathway inhibition must be sustained for at least 45% of the dosing interval to produce 30% tumour regression in the Rat1-myr-p110α tumour-bearing nude mice.

To assess the relative PI3K selectivity *in vivo*, BYL719 was tested in a corresponding Rat1-myr-p110δ model. BYL719, when tested at the optimal dose of 50 mg/kg p.o., every day, showed only a modest antitumor effect (T/C of 30%) and it did not achieve 80% inhibition of AKT phosphorylation (*in vivo* IC_{80} = 29 µmol/L; corrected for BYL719 plasma protein binding in mouse IC_{80} = 2,552 mmol/L) most likely explaining the modest anti-tumour effect observed and in line with the modest activity of the compound on p110δ.

PK/PD and anti-tumour activity of alpelisib in breast cancer

The PK/PD relationship of alpelisib was assessed in the BT-474 luminal B breast tumour bearing mice model which harbours a K111N mutation in PIK3CA and ERBB2 amplification. Each female athymic mouse received a single oral dose of 50 mg/kg alpelisib.

Tumours were collected for *in vivo* PK and PD analysis (Ser473P-Akt evaluated qualitatively by Western blot and quantitatively by Reverse protein Array) at different time points. After a single dose administration of 50 mg/kg, alpelisib inhibited 70% or more phosphorylation of Akt at Ser473 up to 6h. Inhibition at 8h was slightly less pronounced, which corresponded to the decrease in concentration of the compound observed in the tumour tissue at that time. Moreover, partial inhibition was still observed at 12 and 16h but the signalling was back to baseline activation levels at 24h.

To determine whether the dose- and time-dependent pathway inhibition was linked to anti-tumour activity, BT-474 tumour-bearing nude mice were treated orally once a day with alpelisib at the doses of

12.5, 25 or 50 mg/kg. Alpelisib administered at 12.5, 25 and 50mg/kg produced a T/C of 30.8, 17.1 and 3.7%, respectively and showed a statistically significant body weight loss of 8.2% at 50 mg/kg.

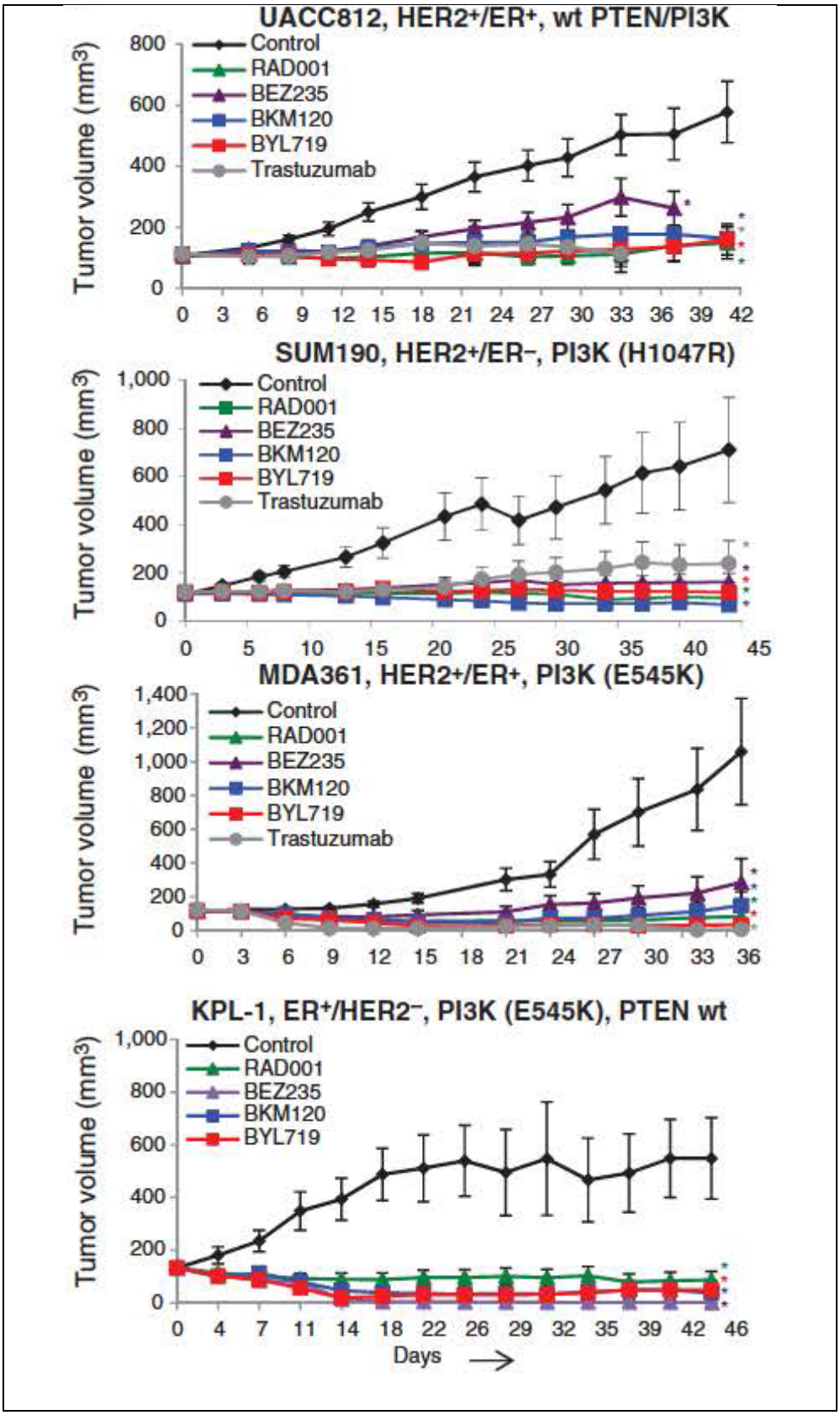
These data were confirmed when alpelisib was administered *in vivo* at the dose of 50 mg/kg (qd, p.o) to different tumour models carrying either a PIK3CA mutation (T47D, MCF7), a PIK3CA mutation and a K-Ras mutation (HCT116), or a protein tyrosine kinase amplification (cMet in GTL16, erbB2 in NCI-N87). BYL719 administered at the optimal dose produced an antitumor effect in all the tumour models tested regardless of their origin (Table 3). A synergistic anti-tumor effect was observed in the HCT116 model when BYL-719 and the MEK inhibitor LFE158-NX were coadministered to nude mice (data not shown).

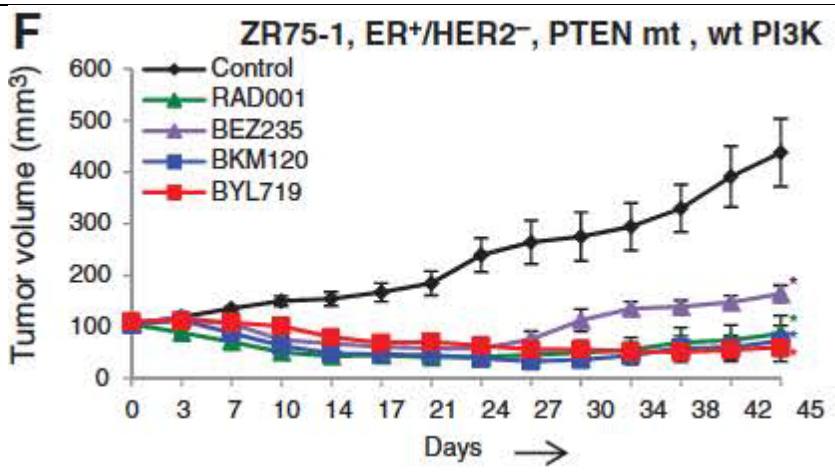
Table 3: Summary of *in vivo* activity of BYL719-NX administered at 50 mg/kg, p.o, daily in disease models compared to the mechanistic model in mouse

Tumor line	Histotype	Genetic alterations (major)	T/C or Regs %
Rat1-myr-HA-p110α°	-	p110α overexpression	-70.7/-65.2
T47D	Breast	*PIK3CA* mutation (H1047R)	-62.6/-54.5
MCF7	Breast	*PIK3CA* mutation (E545K)	1.5
BT-474*	Breast	*PIK3CA* mutation(K111N)/erbB2 amplification	-23/3.7
NCI-H596[&]	Lung	*PIK3CA* mutation(E545K)/EGFR overexpression	-6.1/-6.3
EBC1	Lung	c-met amplification	43.4
NCI-N87	Gastric	erbB2 amplification	-11
GTL-16	Gastric	c-met amplification	14/31.4
HCT116	CRC	*PIK3CA* mutation (H1047R)/ K-Ras mutation	42.4

Summary of the antitumor activity of BYL719 administered at the optimal dose of 50mg/kg, q24h. Regs: Regressions. Positive values correspond to T/C (%); negative values correspond to tumor regressions (%).

The *in vivo* activity of alpelisib (50 mg/kg) was further investigated in five xenograft breast cancer models: SUM190 (ER^- and $Her2^+$), UACC812 ($ER^+$and $Her2^+$), MDA361 ($ER^+$and $Her2^+$), KPL-1 ($ER^+$and $Her2^-$) and ZR75-1 ($ER^+$and $Her2^-$). Its activity was also compared with the antitumoral activity of other PI3K inhibitor (NVP BKM120), an mTORC1 specific inhibitor (NVP RAD001), and a dual PI3K/mTORC1/2 inhibitor (NVP BEZ235). Significant antitumor activity was observed with each of the inhibitors in the five xenograft models (Figure 2).


UACC812, HER2+/ER+, wt PTEN/PI3K
Tumor volume (mm3)
Control
RAD001
BEZ235
BKM120
BYL719
Trastuzumab
SUM190, HER2+/ER−, PI3K (H1047R)
MDA361, HER2+/ER+, PI3K (E545K)
KPL-1, ER+/HER2−, PI3K (E545K), PTEN wt
Days



Mice bearing tumor xenografts from the HER2 amplifies breast cancer cell lines (UACC812, SUM190, MDA361, KPL-1 and ZR75-1) were treated daily orally with BKM120 (35 mg/kg), BYL719 (50 mg/kg), RAD001 (10 mg/kg), BEZ235 (35 mg/kg) or 10 mg/kg trastuzumab by intraperitoneal injection twice per week.

Figure 2: PI3K/mTOR inhibitors show *in vivo* efficacy in mouse xenograft models of multiple subtypes of human breast cancer

Analyses of SUM190 tumours treated daily with each inhibitor revealed that at 2.5 hours after final dose, AKT phosphorylation was significantly reduced at both the Ser473 and Thr308 in BKM120, BYL719 and BEZ235 treated tumours. In contrast, levels of phospho AKT were found to be above that of the vehicle control in RAD001 treated tumours. However, RAD001 did induce significant decreases in pS6S235 236 levels in SUM190 xenografts, consistent with that induced by BKM120, BYL719, and BEZ235. Immunohistochemical analyses of the tissues confirmed these findings; although pAKTS473 levels were decreased in the BKM120, BYL719 and BEZ235 treated tumours, no decrease was observed in the RAD001 treated tumours. RPPA analyses were repeated on samples collected 24 hours after final dose in the UACC812 xenografts. At this time point, pAKTS473/T308 levels were significantly increased in response to each molecule, indicating that feedback activation also occurs *in vivo* with these molecules.

Secondary pharmacodynamic studies

The potential for off-target pharmacology activity of alpelisib was also evaluated against 143 GPCRs, transporters, ion channels, nuclear receptors and enzymes, in binding assays. At a concentration of 10 µM, alpelisib exhibited >50% inhibition against 2 targets, the adenosine Ad3 and serotonin 5HT2A receptors. The IC_{50} values for these receptors were 2.25 µM (Ki=2.15 µM) and 6.7 µM (Ki=4.6 µM), respectively. The results for 5HT2A receptor was found with batch NX-1 but was not confirmed with batch NX-2. Weaker pharmacology activity was also found on the adenosine Ad1 receptor (15 µM, Ki=13 µM) and the phosphodiesterase PDE4d (13 µM).

The IC_{50} values of alpelisib evaluated in these assays were higher than the plasma alpelisib unbound C_{max} of 0.7022 µM observed in patients at maximum recommended therapeutic dose levels of 300 mg QD, suggesting that alpelisib is not likely to have activity against adenosine Ad3, Ad1 and serotonin 5HT2A receptors and the phosphodiesterase PDE4d at exposures achieved in patients.

The PI3K/Akt pathway and more specifically p110α, plays a significant role in glucose metabolism, particularly by mediating glucose transport into adipocytes and muscle tissues. The effects of alpelisib on glucose uptake were assessed in 3T3-L1 differentiated cells. The IC_{50} value obtained in this study

was 169±75 nM. The impact of treatment with alpelisib on glucose homeostasis was assessed in more detail in mice and revealed that insulin plasma levels increased proportionally with alpelisib plasma concentrations, while blood glucose levels were maintained close to normal up to 20 µmol/L of alpelisib. However, above 20 µmol/L, an alpelisib concentration-dependent glucose increase was observed which led to hyperglycaemia despite insulin plasma level elevation.

Safety pharmacology programme

As part of the development program for alpelisib, several stand-alone safety pharmacology studies were conducted. Additionally, cardiovascular system safety pharmacology endpoints were incorporated into study designs for the pivotal repeat-dose toxicity in dog.

Cardiac safety was evaluated *in vitro* and in vivo in stand-alone studies and by monitoring ECGs and vital signs during the PO repeat-dose studies in dogs.

Alpelisib had an IC_{50} value of 9.4 µM in the hERG assay; this concentration is approximately 13-fold higher than the plasma alpelisib unbound C_{max} of 0.7022 µM observed in patients treated with 300 mg QD alpelisib.

No treatment-related ECG effects in dog were noted within 2 and 4 and 13-week repeated oral dose toxicity studies up to 90 mg/kg/day and rising-dose study up to a dose of 180 mg/kg/day. At 90 mg/kg/day, the C_{max} of 40900 ng/mL and 87300 ng/ mL for male and female dogs, respectively, were higher than the C_{max} bound plasma concentration (310 ng/mL) observed in patients treated with 300 mg alpeisib.

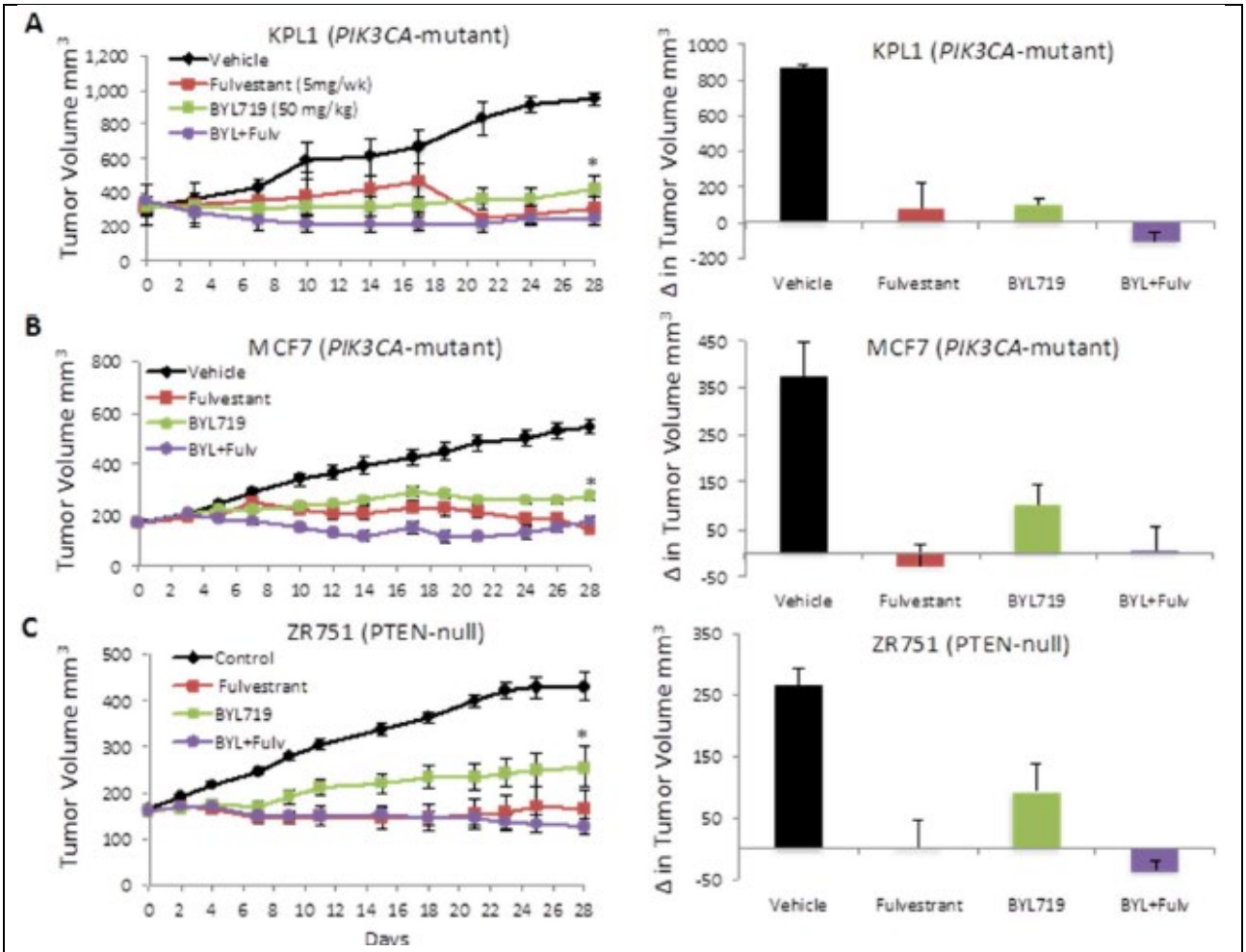
However, *in vivo* oral administration of alpelisib to telemetered male Beagle dogs at single doses of 0, 5, 15 and 30 mg/kg caused a treatment-related dose-independent increase in average systolic and diastolic arterial blood pressure and a persistent decrease in average heart rate at all dosages. These doses corresponded to a C_{max} of 15900-15500 ng/mL, 49400-65100 ng/mL and 72400-74400 ng/mL, respectively, which are at least 50-fold higher than the total plasma C_{max} (310 ng/mL) observed in patients treated with 300 mg alpelisib.

Neuro-functional assessment and motor activity were evaluated in male rats as part of the Functional Observational Battery. A single dose of alpelisib administered via oral at 80 mg/kg did not result in any relevant changes compared to controls. No biologically relevant changes were observed upon respiratory measurements using plethysmography.

Pharmacodynamic drug interactions

Combination with fulvestrant

The activity of single agent BYL719 and combination with endocrine therapy (fulvestrant) was assessed in three cell line models of ER+ breast cancer that carry distinct genetic alterations that confer aberrant PI3K/AKT signalling; KPL1 (PIK3CA mutant), MCF7 (PIK3CA mutant) and ZR751 (PTEN-null). Each of the xenograft models tested was confirmed to be sensitive to endocrine therapy by weekly fulvestrant treatment. Significant anti-tumour activity was also observed with single agent BYL719 (50 mg/kg) and the combination of BYL719 plus fulvestrant in each of the models.



Growth curves and histograms representing the anti-tumor activity of single agent BYL719 or combination with fulvestrant. A, KPL1 (*PIK3CA* mutant), B, MCF7 (*PIK3CA* mutant), C, *ZR751* (PTENnull), D, T47D (*PIK3CA* mutant). BYL719 was given at 50 mg/kg PO daily, Fulvestrant given 5 mg/week by subcutaneous injection in KPL1, MCF7 and ZR751 models. *Represent arms that are statistically different from the vehicle control arm ($p < 0.05$ P-values calculated using a two-way pair Student t-test. Data represent mean +/- SEM

Figure 3: Alpelisib *in vivo* efficacy in ER$^+$ breast cancer

While single agent BYL719 or single agent fulvestrant treatment inhibited tumour progression in all three models, the combination of both molecules induced putative mean tumour regressions in both the PIK3CA mutant KPL1 and PTEN-null ZR751 xenografts. Tolerable levels of body weight loss (<10%) were observed with the single agent or combination treatment arms.

Different treatment dosage of BYL719 (25 mg/kg/day) and fulvestrant (200 mg/kg subcutaneously twice week) were tested in monotherapy and in combination in two well established ER positive/PIK3CAmut xenograft models (MCF7 and T47D cells). Daily administration of BYL719 (25 mg/kg) resulted in modest reduction of tumour growth in both models. Fulvestrant monotherapy (200 mg/kg, twice weekly) was sufficient to prevent further tumour growth and, in some cases, to induce tumour shrinkage. However, the combination of both agents showed marked tumour regression and, in some cases, resulted in complete tumour remissions.

In addition, in a patient-derived xenograft (PDX) model of ER-positive PIK3CA mutant breast cancer where the patient had progressed on multiple lines of endocrine therapy, including fulvestrant, the combination of alpelisib and fulvestrant induced tumour regression as compared to very limited activity for either alpelisib or fulvestrant as single agents.

The *in vivo* activity of alpelisib in combination with fulvestrant was assessed in ER^+ breast cancer cell line xenografts progressing on everolimus (RAD001) or CDK4/6 inhibitors (palbociclib and ribociclib/LEE011).

Mice with tumours progressing on everolimus were randomised into the following treatment groups; 1) continue on 10 mg/kg everolimus, 2) 5 mg/week fulvestrant, 3) 35 mg/kg BYL719 daily or 4) the combination of BYL719 + fulvestrant. In each of these experiments, the control tumours continued to progress on single agent everolimus for the duration of study. Interestingly, tumours that developed resistance to everolimus also appear to display a decreased sensitivity to fulvestrant as well. Treatment with single agent BYL719 was able to slow the progression of these resistant tumours. The combination of BYL719 and fulvestrant induced increased inhibition of tumour progression relative to either single agent in 2 out of the 3 models tested. In the MCF7 (*PIK3CA* mutant) model, tumours continued to progress on everolimus, fulvestrant or BYL719 single agent treatment, however, the combination of BYL719 and fulvestrant induced significant tumour regressions from baseline. Tolerable levels of body weight loss (<10%) were observed with the single agent or combination treatment arms.

Mice with tumours progressing on CDK4/6 inhibitors (palbociclib or ribociclib/LEE011) plus fulvestrant were randomised into the following treatment groups; 1) continue on 75 mg/kg palbociclib plus fulvestrant, 2) switch to 75mg/kg LEE011 plus fulvestrant, 3) or switch to 35 mg/kg BYL719 plus fulvestrant. Control tumours treated with palbociclib plus fulvestrant continued to progress throughout the duration of study, as did xenografts switched to LEE001 plus fulvestrant. However, mice switched from CDK4/6 inhibitor to PI3K-inhibitor showed significant regressions in engrafted tumours. Similarly, ER^+ breast cancer cell line xenografts (HCC1500, *PIK3CA* wild-type) progressing on LEE011 plus fulvestrant showed a significant reduction in the rate of tumour progression when switched to BYL719 plus fulvestrant. Finally, ER^+ breast cancer cell line xenografts that show innate resistance to CDK4/6 inhibition through LEE011 were found to be more sensitive to PI3K-inhibition through BYL719 plus fulvestrant. Body weight loss up to 6.25% was observed in animals treated with the combination of fulvestrant and alpelisib. This combination induced higher decrements in body weighs than the combination of fulvestrant and ribociclib (LEE011) and lower decrements in body weighs than the combination of fulvestrant and palbociclib.

2.3.3. Pharmacokinetics

Pharmacokinetic behaviour of alpelisib was investigated in mouse, rat, dog and human.

Absorption of alpelisib-related material in the rat was estimated to be 62.5% and 53.5% in human. Tmax of alpelisib after single oral dosing was between 0.5 and 2 hours in all species. At highest doses and after multiple doses Tmax reached 3 hours in rats and dogs. The bioavailability of alpelisib in mouse and dog was estimated to be complete (106% and 140% in mouse and dog, respectively).

Following i.v. dosing, blood clearance was low (0.48, 0.594 and 0.429 L/(h·kg)) compared to hepatic blood flow in mouse, rat and dog. The systemic half-life in blood (mouse and dog) and in plasma (rat) was relatively short (2.9, 3.6 and 1.5 hours, respectively). Volume of distribution was moderate (0.93 to 1.8 L/kg) across species.

Alpelisib exposure increased in a dose proportional manner in GLP toxicology studies conducted in rat and dog. Exposure increased up to 2-fold following multiple dosing in rats and no apparent accumulation was observed in dogs. Exposure in rat females was 1.5-2-fold higher than in rat males. No clear gender difference was noted in terms of AUC and Cmax in dogs.

In pregnant rats and rabbits, exposure to alpelisib increased more than dose proportional at lower doses (8 fold between 3 and 10 mg/kg in rats and 6 fold between 3 and 15 mg/kg in dogs) and

approximately dose proportionally at higher doses (3 fold between 10 and 30 mg/kg in rats and 1.7-fold between 15 and 25 mg/kg in dogs).

The plasma protein binding of alpelisib was moderate in mouse (91.24%), rat (90.65%), dog (89.2%) and human (89.2%) with no major species differences.

In rats dosed with radiolabeled alpelisib, radioactivity distributed rapidly throughout the body, with highest tissue concentrations in liver (and bile), kidney, and harderian gland. Tmax in most tissues was achieved at 15 minutes and 1 hour post dose after i.v. and p.o. administration, respectively. The 14C-alpelisib-derived radioactivity observed in the intestinal walls indicated active secretion into the lumen of the GI tract. In pigmented rats specific but reversible binding to melanin-containing structures was observed. No evidence for brain penetration of alpelisib related radioactivity was observed in the QWBA data. Alpelisib passed the placental barrier in rats and rabbits, but foetal plasma concentrations were low (rat approximately 10 fold lower; rabbit approximately 60 fold lower) compared to maternal plasma, most likely due to BCRP expression in the apical membrane of placental syncytiotrophoblasts and the fact that alpelisib is a substrate of this enzyme.

The predominant metabolic pathway observed in rat, dog, and human was amide hydrolysis, forming metabolite BZG791 (M4). Other phase I oxidative metabolism and a minor amount of glucuronidation was observed across species but is expected to play a more minor role in metabolic elimination.

The major component in plasma of rat, dog and human was unchanged alpelisib. The most prominent plasma metabolite was BZG791 which represented 3.0%, 4.61% and 26.7% of the measured AUC in rat, dog and human, respectively. Human exposure to this metabolite, irrespective of fed/fasted status, was covered by the rat, indicating that the metabolite was adequately assessed in the toxicology studies. BZG791 had no relevant contribution to total pharmacological activity in human.

CYP3A4 was the main enzyme involved in the oxidative metabolism of alpelisib to M3 *in vitro*. Alpelisib was only noticeably metabolized by UGT1A9 (among the 13 UDP-glucuronosyltransferase (UGT) isoforms tested) but displayed a low turnover in glucuronidation in general. Alpelisib hydrolysis to BZG791 occurred systemically by spontaneous chemical decomposition and enzymatic hydrolysis via ubiquitously expressed, high-capacity enzymes (esterases, amidases and choline esterase) not limited to the liver. BZG791 can be formed by gastric hydrolysis at low pH but only under prolonged (>3 h) exposure to gastric acid.

Excretion of drug-related material in rat, dog and human was mainly via the faecal route, with a minor contribution by elimination into urine which occurred primarily within the first 24 hours of exposure. Elimination was mainly driven by metabolism but evidence for a sizeable contribution from hepatobiliary export and direct intestinal secretion was obtained from the rat.

Drug-drug interactions

To assess the risk of alpelisib becoming subject to a drug-drug interaction *in vivo*, both the enzymes and transporters that contribute to alpelisib's elimination were identified *in vitro*.

Transporters

The *in vitro* permeability and efflux transporter interaction potential of alpelisib was examined in the Caco-2 cell monolayer model. The apparent permeability (Papp) through Caco-2 was medium-high (Papp (A-B) = 3.84×10-6 cm/s; Papp (B-A) = 18.25×10-6 cm/s), mediated by efflux. Apparent intestinal uptake of alpelisib was examined in the presence and absence of efflux pump inhibitors, showing that only selective inhibitors of BCRP but not inhibitors of P-gp (including cyclosporine A) or MRP2 (Multidrug resistance-associated protein) changed the uptake of alpelisib. Further investigations confirmed that alpelisib was a substrate of BCRP (Km = 2-15 µM) and a very weak substrate of P-gp (Km > 128 µM). In the absence of transporter-mediated efflux, the permeability of alpelisib was high

with a Papp (A-B) of 11.7×10-6 cm/s compared to internal standards in a low efflux Madin-Darby canine kidney cell line (MDCK) permeability assay. Uptake of alpelisib in hepatocytes was shown to be passive in human. Active hepatobiliary disposition of alpelisib (likely via BCRP) was confirmed in sandwich-cultured hepatocytes.

BZG791 was shown to permeate only at a low rate through Caco-2 monolayers (P_{app} = 0.4×10-5 cm/s, Efflux ratio ~145) most likely modulated by two or more efflux transporters (BCRP and MRP2).

Enzyme Induction

Results of *in vitro* induction studies are summarised in Table 4.

Table 4: Enzyme induction by alpelisib and M4

			Alpelisib	M4
CYP1A2	mRNA	EC_{50} (µm)	>10	>100
		Fold induction	2.9	2.7
		% positive control	6.3	7
	activity[a]	EC_{50} (µm)	>10	>100
		Fold induction	1.2	1.5
		% positive control	2.3	4.7
CYP2B6	mRNA	EC_{50} (µm)	3	26
		Fold induction	4.9	3.2
		% positive control	54.3	23
	activity[b]	EC_{50} (µm)	>10	>100
		Fold induction	1.4	1.4
		% positive control	10.7	4.7
CYP2C9	mRNA	EC_{50} (µm)	2.2	66
		Fold induction	3	2.0
		% positive control	147.3	67
	activity[c]	EC_{50} (µm)	ND	ND
		Fold induction	2.5	1.7
		% positive control	51.7	20.3
CYP3A4	mRNA	EC_{50} (µm)	1.7	>100
		Fold induction	66	4.3
		% positive control	82	6.7
	Activity[d]	EC_{50} (µm)	ND	>100
		Fold induction	2.72	1.1
		% positive control	32	2.3

Data expressed as mean of triplicate samples.
[A] CYP1A2 activity measured by acetaminophen formation
[B] CYP2B6 activity measured by OH-bupropion formation
[c] CYP2C9 activity measured by 4'-hydroxydiclofenac formation
[d] CYP3A4 activity measured by 1'OH-midazolam formation

Enzyme inhibition

In vitro inhibition results are presented below.

Table 5: Inhibitory effect of alpelisib on CYP enzyme-selective metabolic reactions

CYP enzyme	Probe reaction	IC_{50} value (µM)		K_I value (µM) (Inhibition mechanism)	
		Total	Unbound	Total	Unbound
CYP1A2	phenacetin O-deethylation	> 100	> 89	n.i.	
CYP2A6	coumarin 7-hydroxylation	> 100	> 89	n.i.	
CYP2B6	bupropion hydroxylation	> 100	> 92	n.i.	
CYP2C8	paclitaxel 6α-hydroxylation	27 ± 6	24 ± 5	32 ± 2 (full competitive)	28 ± 2
CYP2C9	diclofenac 4'-hydroxylation	42 ± 5	39 ± 5	22 ± 6 (partial mixed)	20 ± 6
CYP2C19	S-mephenytoin 4'-hydroxylation	75 ± 5	59 ± 4	n.i.	
CYP2D6	bufuralol 1'-hydroxylation	> 100	> 89	n.i.	
CYP2E1	chlorzoxazone 6-hydroxylation	> 100	> 79	n.i.	
CYP3A4	midazolam 1'-hydroxylation	> 100	> 92	n.i.	
CYP3A4	testosterone 6β-hydroxylation	> 100	> 89	n.i.	

Table 6: Time dependent inhibitory effect of BYL719 on CYP enzymes

CYP enzyme	Probe reaction	Time-dependent inhibition
CYP1A2	phenacetin O-deethylation	not observed
CYP2C9	diclofenac 4'-hydroxylation	not observed
CYP2D6	bufuralol 1'-hydroxylation	not observed
CYP3A4	midazolam 1'-hydroxylation	K_I = 5.6 ± 1.0 µM k_{inact} = 0.0110 ± 0.0006 min^{-1}

Table 7: Inhibitory effect of BZG791 on CYP enzyme-selective metabolic reactions

CYP enzyme	Probe reaction	IC50 value (µM)	Time-dependent inhibition
CYP1A2	phenacetin O-deethylation	> 100	not observed
CYP2A6	coumarin 7-hydroxylation	> 100	n.i.
CYP2B6	bupropion hydroxylation	> 100	n.i.
CYP2C8	amodiaquine N-deethylation	68 ± 2	n.i.
CYP2C9	diclofenac 4'-hydroxylation	> 100	not observed
CYP2C19	S-mephenytoin 4'-hydroxylation	> 100	n.i.
CYP2D6	bufuralol 1'-hydroxylation	> 100	not observed
CYP2E1	chlorzoxazone 6-hydroxylation	> 100	n.i.
CYP3A4/5	midazolam 1'-hydroxylation	> 100	not observed
CYP3A4/5	testosterone 6β-hydroxylation	> 100	n.i.

n.i.= not investigated

Transporters inhibition

Based on the results of transporter inhibition studies alpelisib was found to be a weak inhibitor of P-gp, BSEP, OATP1B1, OATP1B3, OCT-1, OAT3, and MATE1, with the lowest Ki being observed for OATP1B1 (Ki = 20.9 µM).

BZG791 was found to be a weak inhibitor of BSEP, BCRP, OATP1B3, OCT-1, OAT1, and MATE1, with the lowest Ki for OATP1B3 (Ki= 42.4 µM), a moderate inhibitor of OATP1B1 (Ki = 8.59 µM) and a strong inhibitor of OAT3 (Ki = 1.38 µM).

2.3.4. Toxicology

Alpelisib was tested in a toxicology program consisting of safety pharmacology, acute and subchronic toxicity as well as studies of genotoxicity and reproductive toxicity, in accordance with the ICH S9 Guideline on Nonclinical Evaluation of Anticancer Pharmaceuticals as well as all other relevant ICH Guidelines on Safety (Table 8).

Table 8: Toxicology program with alpelisib

Study type and duration	Route of administration	Species
Single-dose toxicity	po (orally)	Dog
Repeat-dose toxicity		
2 weeks	po	Rat and Dog
4 weeks	po	Rat and Dog
13 weeks	po	Rat and Dog
Reproductive and developmental toxicity		
Embryo-fetal development	po	Rat and Rabbit
Genotoxic potential		
In vitro		Bacterial and mammalian cells
In vitro	po	Rat
Local tolerance		
Contact sensitization	dermal	Mouse
Skin irritation/corrosion	dermal	Rabbit
Phototoxicity		
In vitro		Mammalian cells
Mechanistic studies		
Glucose/insulin tolerance test	po	Mouse
Skin toxicity	po	Rat

Single dose toxicity

In a rising-dose toxicity study in dogs alpelisib was administered to 2 groups of 1 male and 1 female/group dogs at single dosages of 10, 30, 90, and 180 mg/kg. Slight to moderate body weight loss was recorded at ≥ 10 mg/kg, associated with a slightly to severely reduced food consumption and diarrhoea at ≥ 90 mg/kg. Non-invasive telemetry revealed no treatment-related effects on electrocardiographic parameters.

Repeat dose toxicity

Table 9: Summary of findings and NOAELs in rats

Duration (weeks)	Species/Sex/ Number/Group	Dose/Route	NOAEL (mg/kg/day)	Major findings	Study ID/ GLP status
2 weeks	Rats (Wist)/ 5M	Oral, gavage; 0, 5, 15, 50 mg/kg	NA	Reduction of body weight gain. Effects indicating impaired hematopoiesis and disturbance of glucose metabolism. Changes in lymph node, large intestine, spleen, thymus, pancreas and sternum/bone marrow.	0870725 *Non-GLP study*
4 (4 weeks recovery)	Rats(Wist)/ 10M, 10F (recovery: 5M, 5F (vehicle and high dose))	Oral, gavage; 0, 10, 30, 80 → 60 → 30 mg/kg	10 mg/kg*	Reduction of body weight gain. Effects on hemo- and lymphopoiesis, disturbance of glucose and lipid metabolism and changes in endocrine pancreas and estrus-cycle. Alterations of bone and teeth. All effects were, or showed tendency to be, reversible.	0970325 *GLP study*
13 (8 weeks recovery)	Rats(Wist)/ 20M, 20F (recovery: 10M, 10F (vehicle and high dose))	Oral, gavage; 0, 2, 6, 20 mg/kg	2 mg/kg	Reduction of body weight gain and alteration of teeth. Most prominent effects seen were increased insulin and glucose levels, pancreatic islet cell hyperplasia, variation in estrous cycle, reduced haemopoiesis as well as lymphoid depletion. These effects were however subject to reversibility.	1070415 *GLP study*

NA: Not applicable, dose range finding study

* see discussion on non-clinical aspects

2-Week Study in Rats (0870725) (non-GLP)

The purpose of this non-GLP oral toxicity study in rats [Study 0870725] was to obtain initial information on the toxicity of alpelisib after repeated dose administration and aid in the selection of appropriate dose levels for a subsequent repeated dose study [Study 0970325].

Daily oral administration of alpelisib to groups of 5 male rats at dosages of 5, 15 or 50 mg/kg/day was well tolerated at the two lower doses. At 50 mg/kg/day a moderate reduction in body weight development was observed without a parallel reduction in food intake. Haematological changes, characterised by decreases in lymphocytes, eosinophils, basophils and large unstained cells, decreases in reticulocyte count, haemoglobin and/or haematocrit, and a decrease in platelet count, were observed starting at 5 mg/kg/day with only mild decreases in lymphocytes noted in individual animals. All these changes indicate a test item-related effect on haematopoiesis. The decrease in globulin at 50 mg/kg/day might be related to the decrease in lymphocytes (decreased immunoglobulin synthesis). An increase in glucose was observed at ≥5 mg/kg/day, which is suggestive of glucose metabolism impairment consistent with insulin resistance/insensitivity. Other clinical biochemistry changes characterised by a decrease in triglycerides associated with an increase in cholesterol were noted with alpelisib at 50 mg/kg/day and suggest a mild test item related effect on liver function.

Test-item related generally atrophic or degenerative microscopic findings were observed in the mesenteric and mandibular lymph nodes, large intestine, spleen, thymus, pancreas and/or sternum/bone marrow at 15 and 50 mg/kg/day.

Toxicokinetic measurements indicated a dose-proportional increase in exposure and no accumulation of the test item with repeated administration. Plasma exposure to alpelisib after 2 weeks of treatment ranged from 5,330 to 102,000 ng·h/mL in terms of AUC0-24h and from 1,290 to 12,100 ng/mL in terms of Cmax at 5 to 50 mg/kg/day, respectively. Highest plasma concentrations of alpelisib were noted 0.5 or 1 hour post-dose.

In conclusion, daily oral administration of alpelisib to groups of 5 male rats was well tolerated at daily doses of 15 mg/kg. At 50 mg/kg moderate effects on body weight development without concomitant effect on food intake, impaired hemopoiesis, disturbance of glucose metabolism (insulin resistance/insensitivity) were seen. Histopathological changes were observed in lymph nodes, intestine, spleen, thymus, pancreas and/or sternum/bone marrow mainly at 50 mg/kg of alpelisib and in some organs also in animals dosed with 15 mg/kg of alpelisib.

4-Week Study in rats followed by 4 week recovery period (0970325) (GLP)

The purpose of this GLP toxicity study in rats [Study 0970325] was to determine the toxicity of alpelisib after repeated oral administration, aid in the selection of appropriate dose levels for subsequent repeated dose toxicity studies and to support first clinical trials in man.

In this study, alpelisib was administered once daily by oral gavage to groups of 10 male and 10 female rats at dosages of 10, 30 or 80/60/30 mg/kg/day and a dosage volume of 5 mL/kg, for 4 weeks. Additional 5 males and 5 females were included in the control and 80/60/30 mg/kg groups as recovery animals. Upon loss of animals and dose reduction in the high-dose group, animals of this group were reassigned to the recovery group resulting in a final distribution of 9 main-group and 6 recovery animals. At the end of the treatment period, recovery animals were observed for further 4 weeks to investigate the reversibility of treatment related effects. In addition to alpelisib, plasma levels of the main metabolite BZG791 were determined.

Daily administration of 80 mg/kg/day of alpelisib resulted in a marked reduction in food intake with associated body weight loss and necessitated early sacrifice of 2 males and 4 females. The cause of moribundity at 80 mg/kg/day with early sacrifice between day 4 and 8 was related to intestinal toxicity. In addition, severe bone marrow toxicity was seen in these animals. Based on the weight loss in the remaining animals the dose was reduced to 60 mg/kg/day as of day 6 and to 30 mg/kg/day as of day 8.

Daily administration of 30 mg/kg/day of alpelisib resulted in a decrease in overall food intake associated with lack of body weight gain. At 10 mg/kg/day a slight decrease in body weight gain was observed in both sexes and a slight decrease in overall food intake in females only.

In haematology, the decrease in reticulocytes, haemoglobin, haematocrit and/or red blood cell counts and associated alterations in red blood cell indices, as well as the decrease in white blood cell counts and associated alterations in the white blood cell differential in males at 30 mg/kg/day and in females at ≥10 mg/kg/day may reflect a primary effect on hemopoiesis and lymphopoiesis. At 30 mg/kg/day in females and in the early sacrificed individuals there was also evidence of an inflammatory response.

Clinical chemistry evaluations revealed a disturbance in the glucose metabolism at 30 mg/kg/day in males and at ≥10 mg/kg/day in females, as well as a disturbance in lipid metabolism and a possible liver effect at 30 mg/kg/day in both genders.

At terminal necropsy, decreased organ weights associated with a morphological correlate (macroscopic and/or microscopic) were noted in the spleen, thymus and uterus at ≥10 mg/kg/day and in the

prostate and liver at ≥30 mg/kg/day. In addition, decreased weights without morphological correlate were noted at ≥10 mg/kg/day in the pituitary and adrenal (females only) glands, and at ≥30 mg/kg/day in the kidneys, testes and ovaries.

Microscopically, generally dose-dependent changes were noted at ≥10 mg/kg/day in the bone marrow (hypocellularity with congestion/haemorrhage), spleen (decreased hemopoiesis and lymphoid depletion), thymus (lymphoid depletion), lymph nodes (lymphoid depletion and reduced germinal centre development), endocrine pancreas (morphological changes in the islets of Langerhans) and prostate (decreased secretion). Mainly at ≥30 mg/kg/day changes were observed in the vagina (diffuse epithelial atrophy and atypical oestrous cycle phase with uterine atrophy) and pituitary gland (decreased acidophilia in the pars distalis and increased anti-FSH/LH immunoreactivity).

Further dose-dependent changes were noted at ≥30 mg/kg/day in the femoral/tibial (knee joint) and sternal growth plate (thickening and decreased metaphyseal trabecular bone density), in incisors (mainly odontoblast degeneration with dentin thinning and pulpa necrosis), in tongue, esophagus, larynx and forestomach (diffuse epithelial atrophy), in skin and mammary area (epidermal atrophy in females and diffuse mammary gland atrophy) and in lacrimal glands (diffuse acinar atrophy).

In addition, secondary treatment-related findings were noted at ≥30 mg/kg/day in the liver (glycogen decrease), exocrine pancreas (decrease of zymogen granules), seminal vesicles (decreased secretion) and Harderian glands (glandular dilatation).

At the end of the recovery period all findings were fully reversible or showed a tendency towards reversibility (no full reversion was seen in low prostate and uterus weights, in reduced plasma triglyceride levels in some females, and in some blood parameters (mean corpuscular haemoglobin concentration, reduced white blood cell, lymphocyte and basophil counts, increased insulin with associated microscopic findings in hemolymphopoietic organs) of both genders).

No distinct gender difference was observed in terms of exposure to alpelisib and its metabolite BZG791. Plasma exposure to alpelisib after 4 weeks of treatment with 10 or 30 mg/kg/day ranged from 23,300/28,800 to 133,000/101,000 ng·h/mL in terms of AUC0-24h and from 3,080/4,730 to 9,200/8,950 ng/mL in terms of Cmax for males/females, respectively. Corresponding plasma exposure to the metabolite BZG791 (M4) ranged from 1340/991 to 8330/3560 ng·h/mL in terms of AUC0-24h and from 195/125 to 654/298 ng/mL in terms of Cmax for males/females, respectively. Highest plasma concentrations of alpelisib and BZG791 were mainly noted 1 or 3 hours post-dose.

In conclusion, administration of alpelisib to male and female Wistar rats at daily oral doses of 80 mg/kg/day was not tolerated as indicated by marked body weight loss and the need for early sacrifice of 6 of 30 animals. A reduction to 60 mg/kg/day did not adequately improve this situation and thus the dose was reduced to 30 mg/kg of alpelisib. This dose was tolerated, but animals did not gain body weight. At 10 mg/kg/day body weight was slightly reduced and clinical pathology and/or post-mortem evaluation established an effect on hemo- and lymphopoiesis, disturbances in the glucose and lipid metabolisms, as well as changes in endocrine pancreas and estrus cycle. Additional morphological alterations at ≥30 mg/kg/day were observed in bones, teeth and organs/tissues with an epithelial/glandular structure. Clinical pathology changes indicated also an inflammatory response. In general, the changes observed macro- or microscopically were fully reversible after 4 weeks of treatment cessation, or showed a tendency toward reversibility but no full recovery (i.e. effects on the hemo/lymphopoietic systems).

A NOAEL of 10 mg/kg/day was proposed based on the above (see discussion on non-clinical aspects).

13-Week Study in Rats (including micronucleus assay) followed by an 8 week recovery period (1070415) (GLP)

The objective of this GLP toxicity study in rats [Study 1070415] was to determine the toxicity of alpelisib following daily oral (gavage) administration to the rat for 13 weeks. An assessment of delayed onset toxicity and / or reversibility of toxicity was made during an 8-week treatment-free period. The toxicokinetic profile of the test article was also assessed. The study also included a micronucleus assay in peripheral blood.

In this study, alpelisib was administered by oral gavage to three groups of rats (20 or 30/sex/group) at daily doses of 2, 6 or 20 mg/kg/day for at least 13 weeks. Another group of rats (30/sex) received vehicle at an equivalent dosing volume of 5 mL/kg and served as controls. Ten animals per sex in the 20 mg/kg/day group and in the control group were maintained on study for an 8-week recovery period.

There were no deaths related to effects of alpelisib. There were no test article-related clinical signs, with the exception of a number of females at 20 mg/kg/day which had pale teeth. Mean body weight gain was dose-dependently decreased at ≥6 mg/kg/day in males and females. Group mean food consumption was slightly decreased at 20 mg/kg/day.

Clinical pathology evaluations revealed dose-related and reversible, mildly to moderately lower absolute lymphocyte counts at ≥6 mg/kg/day correlating with the microscopic finding of lymphoid depletion in several lymphoid tissues. Minimally to markedly higher insulin concentrations at all dose levels on Days 1 and 75 of the dosing phase were evident in response to variably higher glucose concentrations. Increased insulin concentrations were clearly dose-related. However, findings suggested that impaired glucose uptake was generally adequately compensated by secondary insulin release to control increased blood glucose levels, and the effect was reversible after treatment cessation. Higher insulin concentrations correlated with the microscopic finding of pancreatic islet cell hyperplasia at ≥6 mg/kg/day. Most other alpelisib-related clinical chemistry effects (changes in aspartate aminotransferase, alkaline phosphatase, total bilirubin, lipase, amylase, triglycerides, cholesterol, total protein, albumin, globulin, creatinine and electrolytes, generally at 6 or 20 mg/kg/day) were very small, showed reversibility at the end of the recovery period and none were associated with clearly correlating microscopic findings. Urinalysis revealed, at 20 mg/kg/day, mildly lower urine specific gravity and for males only lower urine pH, which had no correlating microscopic findings and showed reversibility at the end of the recovery period.

In this study, the determination of micronucleus frequencies in peripheral blood reticulocytes was integrated, as an endpoint to assess *in vivo* genotoxicity. No statistically significant difference between the mean micronucleus frequencies in the treated groups and the negative control group was seen and furthermore, no significant difference in the trend test was observed.

At the end of the treatment period, there were organ weight reductions when compared with concurrent controls in the spleen, thymus and pituitary gland, which generally correlated with microscopic findings. Upon macroscopic examination, pale incisor teeth were noted in several females at 20 mg/kg/day and there was also a reduction in uterine distension at this dose level. Upon microscopic examination, there was minor lymphoid depletion and reduced haemopoiesis in haemolymphoreticular tissues, islet cell hyperplasia in pancreas, decreased cytoplasmic eosinophilia in pituitary gland and reduced/irregular dentin in incisor teeth of both sexes, along with reduced hyaline droplets in male kidney, adnexal atrophy in female skin and minor variations in the oestrous cycle in the uterus, related to treatment with alpelisib at 6 or 20 mg/kg/day.

At the end of the treatment-free period, findings indicated reversibility of the post-mortem changes recorded at the terminal examination of organ weights and macroscopic findings. There was total reversal of the microscopic changes in the majority of tissues and a trend was observed towards recovery of the microscopic changes in pancreas, mesenteric lymph nodes and to a lesser extent in bone marrow in femur and sternum. Plasma exposure at dose levels between 2 and 20 mg/kg/day alpelisib on Day 75 of treatment ranged from 2,360/4,250 to 41,900/60,300 ng·h/mL in terms of AUC0-24h and from 436/725 to 5070/6740 ng/mL in terms of Cmax for males/females, respectively. Highest plasma concentrations of alpelisib were mainly noted 0.5 or 1 hour post-dose.

In conclusion, the daily oral gavage administration of alpelisib to male and female Wistar rats at dose levels of 2, 6 or 20 mg/kg/day for 13 weeks was generally well tolerated with only minor clinical signs (pale teeth) in high-dose females and decreased body weight gain at 6 and 20 mg/kg/day. Reversible major clinical pathology changes included decreased lymphocyte count, and increased insulin and glucose levels. Mostly minimal to slight treatment-related microscopic findings at 6 or 20 mg/kg/day in the haemolymphoreticular tissues, pancreas, pituitary gland and incisor teeth of both sexes, along with male kidney, female skin and minor variation in oestrous cycle in uterus were generally reversible or showed a trend towards reversibility. Furthermore, alpelisib did not induce an increase in micronuclei in peripheral blood reticulocytes after 4 weeks of treatment. Based on the above results, the low dose of 2 mg/kg/day was considered to be the 'No Observed Adverse Effect Level' (NOAEL).

Genotoxicity

Table 10: Summary of genotoxicity studies

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/ equivocal**
Bacterial reverse mutation assay/ Study 0970323 (GLP) **alpelisib**	Salmonella strains *S. typhimurium*, TA 97a, 98, 100, 102, 1535	0.96-3000 μg/plate with precipitate ≤ 600 μg/plate. (+/- S9)	Negative
Bacterial reverse mutation assay/ Study 1270732 (GLP) **BZG791 (M4/536-12)**	Salmonella strains S. typhimurium, TA 97a, 98, 100, 102, 1535	5-5000 μg/plate (+/- S9)	Negative
In vitro Micronucleus test/ Study 0814071 (non-GLP) **alpelisib**	TK6 human lymphoblastoid cells	3h +S9: 35-280 μg/ml 3h -S9: 86.2-185.7 μg/ml 20h -S9: 2.2-17.5 μg/ml	Negative
In vitro Micronucleus test/ Study 1270733 (GLP) **BZG791 (M4/536-12)**	Human peripheral blood lymphocytes	3h +S9: 191-443 μg/ml 3h -S9: 191-443 μg/ml 28h -S9: 191-443 μg/ml	Negative
In vitro mammalian chromosome aberration test/ Study 0970322 (GLP) **alpelisib**	Human peripheral blood lymphocytes	3h +S9: 20-150 μg/ml 3h -S9: 60-200 μg/ml 20h -S9: 10-25 μg/ml	Negative
Mammalian erythrocyte micronucleus test/ Study 1070415 (GLP) **alpelisib**	Wistar rats, micronuclei in bone marrow	2, 6, 20 mg/kg	Negative

Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects)

Reproduction Toxicity

A GLP embryofetal toxicity study in rat and a non-GLP embryofetal toxicity extended dose-range finding study in rabbit were conducted in order to elucidate effects on the developing foetus. Effects on fertility were also found in the repeat dose studies in rat and dog, which is briefly referred in this section. The findings are summarised in

Table 11.

Table 11: Summary of studies on fertility and reproduction toxicity

Study type/ Study ID / GLP	**Species; Number Sex/ group**	**Route & dose**	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
Male fertility/ 0970324/GLP	Dogs (Beagle)/ 3M, 3F (recovery: 2M, 2F (vehicle and high dose))	Oral, gavage; 0, 2, 5 or 15 mg/kg	4 (4 weeks recovery)	Prostate atrophy and testicular hypocellularity correlating with glandular atrophy	5 mg/kg;
Female fertility/ 0970325/GLP	Rats(Wist)/ 10M, 10F (recovery: 5M, 5F (vehicle and high dose))	Oral, gavage; 0, 10, 30, 80 → 60 → 30 mg/kg	4 (4 weeks recovery)	Vaginal atrophy and oestrus cycle variations associated with uterine atrophy	10 mg/kg
Embryo-fœtal development 1770537/GLP	Rats(Wist)/ 20F	Oral gavage; 3, 10, 30 mg/kg/day	GD 6 to 17	Reduced body weight in dams and implantation losses. Reduced foetal body weight and skeletal malformations.	F0: 3 mg/kg F1: 3 mg/kg
Embryo-fœtal development	(NZW)SPF rabbits Phase I: 3F Phase 2: 3F (+ additional 3 at 25 mg/kg/day)	Oral gavage; Phase I: 3, 10, 30 mg/kg/day Phase II: 3, 10, 25 mg/kg/day	GD 7 to 20	Reduced body weight in dams and implantation losses. Reduced foetal body weight, misshapen head and tail malformations.	F0: 15 mg/kg F1: 3 mg/kg

Toxicokinetic data

Table 12: Overview of toxicokinetic studies with alpelisib

Species (reference)	Gender (n)	Matrix	Dose [a] (mg base/kg)	Tmax (h)	Cmax (ng/mL)	Cmax/ dose (ng/mL)/ (mg/kg)	AUC [b] (ng·h/mL)	AUC interval (h)	AUC [b]/dose (ng·h/mL)/(mg/kg)	T1/2 (h)	CL/F (L/h)	Vz/F (L)	F (%)
Mouse (RD-2009-00574)	f (3 per timepoint)	blood	3.0	2	686	229	6376 (AUCinf)	-	2125 (AUCinf)	-	-	-	106
Rat (DMPK R0900118)	m (4)	plasma	49.9 [c]	0.5	4006	80.1	41097	24	822	-	-	-	-
	m (4)	plasma	50 [d]	0.75	5609	112	59405	24	1188	-	-	-	-
Rat (DMPK R0900368)	m (3)	plasma	15.4	0.5	1280	83.0	14348	24	945	-	-	-	57.3

Dog (DMPK R1300123)	m (3)	plasma	5.01	1.0	1523	304	11655	72	2326	6.23	-	-	-
Dog (RD-2009-00575)	m (3)	blood	0.6	1.7	284	474	1802 (AUCinf)	-	3003 (AUCinf)	-	-	-	140
Dog (DMPK R1000604)	m (4)	plasma	5.06 e)	2.0	1620	316	13400	48	2600	5.7	-	-	-
	m (4)	plasma	5.07 f)	2.0	2020	395	15700	48	3090	4.89	-	-	-
	m (4)	plasma	5.13 g)	2.0	1580	304	13200	48	2530	5.07	-	-	-
Human (Study X2107)	m (4)	plasma	4.80 h)	2.0 k)	1320	275	11100	120	2313	13.7	39.0	838	-

a) a) if not stated otherwise, alpelisib was administered as free base (MW 441.47 g/mol). Concentrations reported in molar units were converted to ng/mL to allow comparison between studies.

b) AUC_{last} unless otherwise stated

c) Dosed as an aqueous suspension in 0.5% methylcellulose

d) Dosed as a solid dispersion formulation

e) Dosed as film coated tablet formulation 1. It was a reference film coated tablet (current CSF), manufactured with jet milled drug substance and surfactant (Batch no. X092 0310).

f) Dosed as film coated tablet formulation 2. It was a film coated tablet optimized for stability, manufactured with jet milled drug substance without surfactant (Batch no.12551.002).

g) Dosed as film coated tablet formulation 3. It was a tablet optimized (same formulation as formulation 2 but with coarser pin milled drug substance) (Batch no. 12551.003).

h) 400 mg dose, mean body weight 83.4 kg

i) Dosed as a solution in 1-methyl-pyrrolidone (NMP) / PEG 300 / Solutol HS15 / Water (10:30:20:40 V/V)

j) Dosed as a suspension in 0.5% (W/V) carboxymethyl cellulose (CMC) / 10% (v/v) Tween 80 (95:5 V/V)

k) Median

Local Tolerance

Assessment of contact sensitizing potential with the murine local lymph node assay (LLNA TIER I)

In this study, 6 female mice per group received topical test or control items on the dorsum of both ears once a day on 3 consecutive days. Auricular lymph nodes were taken 24 hours after the last application. Endpoints were visual examination ears and sizes ear-draining lymph nodes, body weight at treatment start and day of necropsy, ear weight (skin irritation), ear-draining lymph node weights and cell counts (LN hyperplasia). Concentrations used were vehicle control Dimethyl formamide, positive control DNCB (1-Chloro-2,4-Dinitrobenzene): 0.5% (w/w), and alpelisib: 5%, 0.5%, 0.05% (w/w).

Alpelisib did not cause any relevant changes in ear weight, LN weight or LN count up to a concentration of 5% in Dimethyl formamide.

Primary skin irritation/corrosion study in the rabbit

Each animal was treated by dermal application of 0.5 g of the test substance. The test substance was moistened with 0.4 mL of the vehicle and applied to the skin of one flank, using a metalline patch of 2x3 cm. Four hours after the application, the dressing was removed, and the skin cleaned of residual test substance using tap water. The skin reactions were assessed at approximately 1, 24, 48 and 72 hours after the removal of the dressings and test substance. The irritation scores and a description of all other (local) effects were recorded. Adjacent areas of the untreated skin of each animal served as controls.

The study was performed in a stepwise manner and was started by treatment of a single rabbit (sentinel). Two other animals were treated in a similar manner one week later, after considering the degree of skin irritation observed in the first animal.

After treatment with alpelisib, no evidence of skin irritation or corrosion, and no signs of systemic toxicity were observed.

Other toxicity studies

In vitro 3T3 NRU Phototoxicity Profiling Assay

The test was based on the mouse Balb/c 3T3 fibroblast cell line. One group of cells treated with the test item was irradiated with artificial sunlight for 50 min. The other group of cells treated with test item was kept in the dark for 50 min. After approximately 24 hours recovery the cell culture viability was assessed using the Neutral Red Uptake endpoint. The concentration-response curves obtained with and without irradiation were compared regarding the two EC_{50} values (Photo Irritation Factor, PIF) or, alternatively, using the solubility limit during incubation as a surrogate. In parallel, the known phototoxic compound chlorpromazine was tested. Concentration response curves were obtained for the test items with and without irradiation in at least two independent experiments (usually considered dose-range finder and main experiment). With or without irradiation, an EC_{50} of ca. 175 µM was determined, which resulted in a photo-irritation factor (PIF) of 1, indicative of the absence of a phototoxic potential.

In Vitro Balb/c 3T3 Neutral Red Uptake Phototoxicity Assay

Balb/c 3T3 fibroblast cells seeded into 96 well micro-titre plates were treated with a range of concentrations of alpelisib or positive control chemical (Chlorpromazine, CPZ).

The highest concentration prepared was 1000 µg/mL (the maximum as recommended for this assay, according to current regulatory guidelines), however precipitation was noted at concentrations of 316 and 1000 µg/mL upon addition to Hank's balanced salt solution (HBSS). Vehicle control (1% anhydrous analytical grade dimethyl sulphoxide (DMSO) in HBSS) treatments, untreated control (HBSS) treatments and blanks were also included on each plate.

Treatment of cultures with alpelisib resulted in a minimal decrease in cell survival, both in the absence and in presence of irradiation. The survival curves were generally similar and there were no marked differences in neutral red uptake in the presence of irradiation when compared to those in the absence of irradiation. The cell survival at the highest non-precipitating concentration analysed (100 µg/mL) was more than 50% and hence IC_{50} and PIF values could not be calculated. Due to the absence of cytotoxicity up to the highest nonprecipitating concentrations (316 and 1000 µg/mL) no IC_{50} values (with and without irradiation) and, thus, no PIF values have been calculated. Alpelisib was therefore deemed to have no phototoxic potential in this test.

4-week oral (gavage) investigative skin toxicity study in female Brown Norway rats

The purpose of this non-GLP study was to investigate the toxicological effects of alpelisib on the skin when administered to female Brown Norway (BN) rats for 4 weeks. 50 mg/kg alpelisib was administered orally via gavage once daily for 4 weeks to 10 female Brown Norway rats. A corresponding control group of 10 female Brown Norway rats received vehicle only at an equivalent dose volume (5 mL/kg).

The 50 mg/kg/day dose was tolerated for the 4 week dosing period. Body weight loss occurred in all of the alpelisib-treated rats throughout the dosing period. The most significant haematology changes reflected the presence of inflammation (characterized by increases in white blood cell, neutrophil,

lymphocyte and monocyte counts, increases in plasma fibrinogen concentrations) and decreased red blood cell mass (characterized by decreases in red blood cell count, haemoglobin concentration and haematocrit) with an accompanying increase in reticulocyte counts. Other changes were less specific including increases in serum ALT and ALP activities, increased serum urea and cholesterol concentrations and decreased serum albumin, serum triglyceride concentrations.

The mean weights of all three lymph nodes (axillary, auricular, and inguinal) were minimally higher compared to control animals.

Clinical signs related to the skin were the only test article-related clinical observations and included discolored skin, flakey skin, crusty skin, localized hair loss, scabs, scratches, abrasions, wounds, red ears and/or swellings. The onset of these signs was generally after 3 weeks of dosing with continuation until necropsy. The lesions were most commonly located on the ears, head, neck and back.

Test-article-related microscopic findings were observed in the skin and lymph nodes. In the skin, findings from the central zone correlated with the clinically and macroscopically observed lesions (ulceration/erosions). In the periphery of macroscopic lesions (clinically normal skin), minimal to slight hydropic degeneration of basal epithelial cells in hair follicles and the epidermis as well as minimal exocytosis were observed. Minimal to slight dermal infiltration of mononuclear cells was observed with a perivascular and follicular pattern.

In samples from the central region of macroscopic lesions, the dermal and follicular infiltrations of mostly mononuclear cells were more severe (minimal to marked) and extensive ulceration (slight to severe) with fibrinous exudate and crust formation, bacterial colonies and infiltrations of large numbers of neutrophilic granulocytes were observed. In addition, there was slight to moderate epidermal hyperplasia and hyperkeratosis. Besides the mononuclear cell infiltration, there was also minimal to slight proliferation of fibroblasts and minimal dermal oedema.

Finally, none of the treated animals had anagen hair follicles present in the skin compared to their presence in 5 out of 10 control animals.

In lymph nodes (axillary and inguinal), the incidence of absence of germinal centers was higher in treated animals and there was a higher incidence of cortical atrophy.

Since histopathological examination of the skin samples identified mononuclear cell infiltration in the deeper dermis (mostly with a perivascular and follicular pattern), immunohistochemical markers of the immune system were used to characterize these infiltrated mononuclear cells. The infiltrating cells were mainly $CD68^+$ macrophages, $CD163^+$, T cells (identified by CD3 staining) and $CD8^+$. In the macroscopically normal and lesioned skin of BYL719 treated animals, the $CD8^+$ cells were a mix of cells with round or elongated shape, suggesting different $CD8^+$ cell subsets.

BYL719 induced major transcriptional changes in the (dorsal) skin of Brown Norway rats after 4 weeks of daily treatment at 50 mg/kg. Gene expression changes in macroscopically normal and in lesioned skin support immunostimulatory effects (e.g. increased expression of various cytokine and chemokine genes, up-regulated macrophage activation, NK cell, interferon, MHC class I, and ubiquitin/proteasome signatures) as well as skin regenerative processes (e.g. increased activated basal keratinocyte and cell division gene signatures).

In addition to standard procedures used in this study, auricular, inguinal and axillary lymph nodes were collected at necropsy for immunophenotyping. Alpelisib increased T cytotoxic cell, atypically-large lymphoid cells, NK and NKT cells and monocytes in the lymph nodes of the three regions. Furthermore, B cells and some myeloid subsets, including the majority pool of macrophages, dendritic cells and granulocytes were also activated in lymph nodes, as detected by increased MHC-II and/or ICAM-1expression.

Alpelisib-related serum cytokine changes are consistent with skin inflammation and hypersensitivity. The earliest mediator increases were seen in fractalkine (a potent immune cell chemoattractant) and leptin, which promotes and was followed by increases in MCP-1, IP-10, IL-17, VEGF, IL-18, MIP-1α, RANTES, TNFα and IL-12, and decreases in the neutrophil chemoattractant, LIX.

At the 50 mg/kg/day level, the concentrations of BYL719 in female rat plasma measured for the female rats at 2 h post dose on Day 29 was 11.6 µg/ml.

2.3.5. Ecotoxicity/environmental risk assessment

Table 13: Summary of main study results

Substance (INN/Invented Name): Alpelisib					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Pow = 3.04 at pH 5 log Pow = 3.03 at pH 7 log Pow = 3.03 at pH 9			Potential PBT (N)
PBT-assessment					
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.5	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 263 mL/g and 525 mL/g $K_{oc\ soil}$ = 1642 mL/g, 3873 mL/g and 1087 mL/g			
Ready Biodegradability Test	OECD 301	Not inherently biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ (water,\ 12\ ^oC)}$= 15.8-19.7 $DT_{50\ (sediment,\ 12\ ^oC)}$ =107.0-186.0 $DT_{50\ (whole\ system,\ 12\ ^oC)}$ = 47.4-138.0 % shifting to sediment (river)= 51.3% at day 32 (parent) 29.8 % at day 102 (parent) % shifting to sediment (pond)= 27.7% at day 14 (parent) 9.3 % at day 102 (parent)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	5.6	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.48	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	0.30	mg/L	*Danio rerio*

Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCFss (low dose)	1.75	L/kg	%lipids:
	OECD 305	BCFss (high dose)	2.05	L/kg	%lipids:
Sediment dwelling organism	OECD 218	NOEC	64	mg/kg	*Chironomus riparius*

Alpelisib is not a PBT substance. Considering the above data, alpelisib is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The results of the *in vitro* studies showed that alpelisib is a specific p110α inhibitor and inhibits the effects mediated by this kinase as phosphorylation of AKT and AKT downstream effectors (GSK3β and p70S6K). Moreover, alpelisib showed markedly selective efficacy in PIK3CA mutated cell lines when compared to will-type cell lines and when compared to pan-PI3K inhibitors.

In biochemical assays, BZG791, the primary circulating metabolite of alpelisib, was over 500-fold less potent than alpelisib on p110α, over 4-fold less potent than alpelisib on the other class I PI3K lipid kinases and, similar to alpelisib, BZG791 was not active on Vps34 and mTOR. Mechanistic cell-based assays confirmed BZG791 shows no activity on the p110α, p110β and p110δ isoforms.

Pharmacology *in vivo* studies supported the higher affinity of alpelisib on p110α observed in *in vitro* experiments and demonstrated its antitumoral activity in relevant breast tumour xenograft models. Alpelisib also showed anti-tumoural activity in models of lung, gastric or colorectal cancer with PIK3CA mutations or protein tyrosine kinase amplification.

Secondary pharmacology studies suggest that alpelisib is not likely to have activity against other 143 GPCRs, transporters, ion channels, nuclear receptors and enzymes in binding assays.

The PI3K pathway has been shown to play a significant role in glucose metabolism, particularly by mediating glucose transport into adipocytes and muscle tissues and in VEGF regulated permeability of blood vessels. Insulin resistance, hyperglycaemia, inhibition of VEGF signalling and neovascularisation have been associated with alpelisib treatment.

The impact of treatment with alpelisib on glucose homeostasis was assessed. In mice, insulin plasma levels increased proportionally with alpelisib plasma concentrations, while blood glucose levels were maintained close to normal up to 20 µmol/L of alpelisib. However, above 20 µmol/L, an alpelisib concentration-dependent glucose increase was observed which led to hyperglycaemia despite insulin plasma level elevation. In the toxicology studies, alpelisib interfered with glucose/insulin homeostasis in all species investigated (mouse, rat and dog) and in both genders. This was evidenced by elevated basal plasma insulin and glucose concentrations and increased insulin and glucose excursions after glucose or insulin challenges in mice. In rats, insulin and glucose fluctuations were seen, associated with fructosamine elevations, which is a marker for prolonged hyperglycaemia, with a similar but less prominent effect in dogs. In line with this activity, pancreatic cytoplasmic changes or hyperplasia/hypertrophy of the Langerhans islet cells, indicative of cellular activation, were observed in mice and rats. In general, peripheral insulin and glucose effects, which occurred at therapeutically active plasma exposure levels, were reversible after treatment cessation.

Several stand-alone safety pharmacology studies were provided. Furthermore, cardiovascular system safety pharmacology endpoints were incorporated into study designs for the pivotal repeat-dose toxicity in dog. This approach is consistent with ICH S9.

In vitro inhibition of hERG channels (IC_{50} of 9.4 µM) was shown at concentrations ~13-fold higher than the exposure in humans, at the recommended dose of 300 mg/day. No relevant electrophysiological effect was seen in dogs (see SmPC section 5.3).

Based on the available results, it is considered that there is a negligible risk of an electrophysiological effect of alpelisib. However, alpelisib caused an increase in blood pressure and a persistent decrease in average heart rate. In addition, an inhibition of the phosphoinositide 3-kinase (PI3K) signalling pathway has been identified as another cause of drug-induced long QT syndrome via an inhibition of cardiac potassium currents (IKr, IKs) and an increase of the cardiac late sodium current (Lu et al. 2012, Yang et al. 2014; reviews in Ballou et al. 2015, Cohen et al. 2017). Nevertheless, given the absence of (non)clinical evidence of QTc interval prolongation further studies to assess the effect of alpelisib on additional cardiac ion channels and its potential to induce Torsades de Pointes (TdP) cardiac arrhythmias are not required.

Alpelisib administered to male Wistar rats at a single oral dose of 80 mg/kg did not induce toxicologically significant effects on the nervous or respiratory system.

Considering the wide role of the PI3K pathway, both as part of oncogenic development but also as a potential mechanism of resistance to several therapies used as standard of care; alpelisib has been explored in combination with several other targeted therapies such as EGFR inhibitors or CDK inhibitors, endocrine therapies or various cytotoxic therapies, such cisplatin or radiation. In breast cancer models, non-clinical studies were conducted with alpelisib in combination with the aromatase inhibitor letrozole, the ER antagonist fulvestrant, the CDK4/6 inhibitor ribociclib, the anti-HER2 therapy trastuzumab, and the mTOR inhibitor. In all cases the combination of alpelisib and other therapeutic agent was superior to single-agent treatment (data not shown).

The combination of alpelisib with fulvestrant showed to be more effective than the monotherapy in ER^+ breast cancer cell line xenografts with PIK3CA mutation (MCF7, KPL1, and T47D) or PTEN-null (ZR751), in a PDX model of ER^+ PIK3CA mutant breast cancer where the patient had progressed on multiple lines of endocrine therapy, including fulvestrant, in ER^+ breast cancer cell line xenografts progressing on everolimus (mTORC1) or CDK4/6 inhibitor (palbociclib or ribociclib/LEE011) treatments. Despite differences in tumour volumes between fulvestrant and combination groups were not always statistically significant, the clinical relevance of these differences have been already investigated in the pivotal phase III clinical trial. Regarding the safety, body weight loss (<10%) were observed with the single agent or combination treatment in all treated animals.

Pharmacokinetic behaviour of alpelisib was investigated in mouse, rat, dog and human. The similarities in the *in vitro* and *in vivo* pharmacokinetic profile between rat, dog and human support the adequacy of these species for toxicological assessment of alpelisib.

Based on the results of metabolic *in vitro* induction and inhibition studies, alpelisib may induce the metabolic clearance of co-administered medicinal products metabolised by CYP2B6, CYP2C9 and CYP3A and may inhibit the metabolic clearance of co-administered medicinal products metabolised by CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (time-dependent inhibition) if sufficiently high concentrations are achieved *in vivo* (see SmPC section 4.5). In the absence of clinical data on CYP2C9, caution is recommended regarding CYP2C9 substrates with narrow therapeutic index. *In vitro* evaluations indicated that the pharmacological activity of CYP2C9 substrates with a narrow therapeutic index such as warfarin may be reduced by the CYP2C9 induction effects of alpelisib. Furthermore, sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be

used with caution in combination with Piqray, as alpelisib may reduce the clinical activity of such medicinal products. (see SmPC section 4.5).

Inhibition of CYP2C8 by alpelisib at clinically relevant concentrations can be discarded based on the result of a clinical trial that showed that the PK of paclitaxel (a CYP2C8 substrate) was unaffected by alpelisib (see clinical pharmacology).

Since alpelisib is an inducer and an inhibitor of CYP3A4, the effect of alpelisib on CYP3A4 enzymes was investigated by both a clinical DDI study and PBPK simulations and it was concluded that no dose adjustment is required when co-administering Piqray with CYP3A4 substrates (see clinical pharmacology and SmPC sections 4.4 and 4.5).

Alpelisib is a substrate of BCRP (Km = 2-15 µM) and a very weak substrate of P-gp (Km > 128 µM) *in vitro*. BCRP is involved in the hepatobiliary export and intestinal secretion of alpelisib, therefore inhibition of BCRP in the liver and in the intestine during elimination may lead to an increase in systemic exposure of alpelisib. Therefore, caution and monitoring for toxicity are advised during concomitant treatment with inhibitors of BCRP (e.g. eltrombopag, lapatinib, pantoprazole) (see SmPC section 4.5).

Alpelisib showed only weak *in vitro* inhibition towards the ubiquitously expressed efflux transporters (P-gp, BCRP, MRP2, BSEP), solute carrier transporters at the liver inlet (OATP1B1, OATP1B3, OCT1) and solute carrier transporters in the kidney (OAT1, OCT2, MATE1, MATE2K). As unbound systemic steady-state concentrations (or concentrations at the liver inlet) at both the therapeutic dose and maximum tolerated dose are significantly lower than the experimentally determined unbound inhibition constants or IC_{50}, the inhibition will not translate into clinical significance. Due to high alpelisib concentrations in the intestinal lumen, an effect on intestinal P-gp and BCRP cannot be fully excluded. Considering the concentration of alpelisib in kidneys, inhibition of the renal organic anion transporter OAT3 by alpelisib (and/or its metabolite BZG791) cannot be discarded in patients at the therapeutic dose (see SmPC section 5.2).

Considering alpelisib (and/or its metabolite BZG791) has a potential to inhibit the activities of OAT3 drug transporters and intestinal BCRP and P-gp, Piqray should be used with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index because Piqray may increase the exposure of these substrates (see SmPC section 4.5).

The toxicity of alpelisib after repeated oral administration was studied in rats and dogs with dosing up to 13 weeks. The pharmacodynamic target and the major pathways of alpelisib metabolism in humans were all represented in these species. Thus, the choice of rats, and dogs was appropriate for the toxicity evaluation of alpelisib. The design of the studies followed the ICH requirements in terms of duration, number of animals, doses, route and frequency of administration.

In the rat and dog repeated-dose toxicity studies, hematopoietic, lymphopoietic, reproductive and gastrointestinal systems, glucose and lipid metabolisms, skin, adnexal tissues, teeth, bones, kidneys and eyes were identified as systems affected by treatment with alpelisib. Despite effects on lipid and glycogen metabolism would be expected by inhibition of the signal transduction pathway of insulin, disturbances in the lipid metabolism were not associated to alpelisib treatment in clinical studies. Additionally, degenerative effects observed in the incisors of rats can be considered rodent-specific with limited relevance for humans since teeth are permanently growing in rats, but not in humans.

Overall, the majority of the observed alpelisib effects were related to the pharmacological activity of alpelisib as a p110α-specific inhibitor of the PI3K pathway, such as the influence on the glucose homeostasis resulting in hyperglycaemia and the risk of increased blood pressure. The bone marrow and lymphoid tissue, pancreas and some reproductive organs of both genders were the main target organs for adverse effects. Effects on bone marrow and lymphoid tissue were generally reversible on

cessation of treatment. Effects on the pancreas and reproductive organs did not fully reverse but showed a tendency towards reversion (see SmPC section 5.3).

All effects were observed at doses that resulted in total plasma exposure levels lower than those reached in patients treated with the maximum recommended dose and were reversible or showed a tendency towards reversibility after a 4- or 8-week treatment-free recovery period.

A NOAEL of 10 mg/kg/day is not considered sufficiently supported by the current findings in the 4 week repeated dose study in rats due to the effects seen at this dose level, i.e. decrease in body weight gain; mild to moderate decrease in eosinophiles and basophiles, mild decrease in haematocrit and haemoglobin levels; increased glucose, Cl and K; decreased organ weight of spleen, thymus and uterus; several dose-related microscopic organ changes. The NOAEL of 2 mg/kg/day derived from the 13-week study is supported. No adverse events were reported at this dose level.

The main human metabolite, BZG791, was measured in 4 weeks toxicity studies in rats and dogs. Rat and dog exposure to metabolite BZG791 was 1.5 and 0.6 folds respectively human exposure. According to the ICH S9 guideline a separate evaluation of the metabolites is generally not warranted for patients with advanced cancer. Therefore, the metabolite is considered characterised from the non-clinical point of view.

Genotoxicity studies in agreement with ICH S2 (R1) guidance have been submitted, including test for gene mutations, chromosomal aberrations *in vitro* and an *in vivo* micronucleus assay integrated in the 13-week oral repeated-dose study in the rat.

Alpelisib was not mutagenic in a *Salmonella* reverse mutation test, or aneugenic or clastogenic in human cell micronucleus and chromosome aberration tests *in vitro*. *In vivo*, after 4 weeks of oral treatment up to 20 mg/kg/day in rats and clear signs of bone marrow toxicity, alpelisib did not induce an increase of micronuclei in peripheral blood reticulocytes. However, it should be noted that the value of the these studies is limited since the concentrations of alpelisib used in *in vitro* studies were lower than those required in the ICH S2 guideline and systemic exposures to alpelisib achieved in the *in vivo* study were only 2 fold or 1.4 fold higher than therapeutic exposure in adult humans. Therefore, the genotoxicity potential of alpelisib in human cannot be ruled out (see SmPC section 5.3).

According to the specifications, impurity levels are below the qualification thresholds defined in ICH Q3A and ICH Q3B. However, several identified impurities were evaluated in the Ames test as well as referenced from published literature (data not shown). Only four studies on genotoxic potential of impurities were conducted in compliance with GLP. Three of the impurities were tested positive in the non-GLP AMES tests and three impurities were tested negative. However, the tested impurities are either not detectable in the drug substance or controlled via a purging step in the manufacturing process, which ensures amounts of less than 25 ppm for mutagenic impurities at drug substance level based on a treatment duration of up to 10 years and a maximum daily dose of 400 mg alpelisib. Hence, the non-GLP Ames tests are accepted in support of the genotoxic testing of alpelisib.

The applicant justified the lack of carcinogenicity studies according to the ICH S9 guideline. This is considered acceptable also acknowledging that no genotoxic potential has been identified for alpelisib and no hyperproliferative or neoplastic changes were observed in the repeat-dose toxicity studies of up to 13 weeks duration.

Absorption studies with alpelisib showed absorption between 290 – 700 nm (peak at 314 nm) with a molar extinction coefficient above the guideline limit of 1000 L/mol/cm (i.e. 1880 L/mol/cm). However, as two *in vitro* 3T3 NRU phototoxicity tests (OECD TG432, non-GLP/GLP) did not identify a relevant phototoxicity potential for alpelisib, alpelisib is not considered phototoxic (see SmPC section 5.3).

A fertility study in rats has not been performed. However, in repeated dose toxicity studies, adverse effects were observed in reproductive organs, such as vaginal or uterine atrophy and oestrus cycle variations in rats, decreases in prostate and testes weight in rats and dogs and prostate atrophy in dogs at clinically relevant doses based on AUC . Based on these results, alpelisib may impair fertility in males and females of reproductive potential (see SmPC sections 4.6 and 5.3).

As per ICH S9, pre-and postnatal and juvenile toxicology studies are generally not warranted to support marketing of pharmaceuticals for the treatment of patients with advanced cancer.

Embryo-foetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity. In rats and rabbits, following prenatal exposure to alpelisib, increased incidences of pre- and post-implantation losses, reduced foetal weights and increased incidences of foetal abnormalities (enlarged brain ventricle, decreased bone ossification and skeletal malformations) were observed starting at exposures below those in humans at the highest recommended dose of 300 mg, indicating potential clinical relevance (see SmPC section 5.3).

The environmental risk assessment does not indicate a potential risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see SmPC section 6.6).

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data package evaluating the pharmacology and toxicity of alpelisib is considered acceptable to support the marketing authorisation.

2.4. Clinical aspects

2.4.1. 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

Table 14: Overview of key studies and their status

Study/phase/ data cut-off/ status	Population	Data included for	Treatment - combination/ single agent	Treatment dosing schedule	No. of subjects randomized
C2301 [a] Phase III PIK3CA mutant cohort: 12-Jun-2018 (Efficacy), PIK3CA non-mutant cohort: 23-Dec-2016 (Efficacy) 12-Jun-2018 (Safety). Recruitment complete; study ongoing	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease progressed on or after AI treatment	Efficacy and safety	Combination: alpelisib 300 mg plus fulvestrant 500 mg Placebo plus fulvestrant 500 mg	Alpelisib p.o. once daily in 28-day cycle Fulvestrant i.m. on Days 1 and 15 of Cycle 1 and on Day 1 (± 3 days) of every cycle thereafter	572 PIK3CA mutant: 341 PIK3CA non-mutant: 231
X2101 [b] Phase IA 22-Mar-2017 Recruitment complete; study ongoing	Adult subjects with advanced solid malignancies, whose tumors had an alteration of the PIK3CA gene	Safety	Single agent: alpelisib 30, 60, 90, 180, 270, 300, 350, 400, 450 mg	Alpelisib p.o. once daily: Alpelisib p.o. twice daily: 120, 150, 200 mg	134
	HR-positive, HER2-negative breast cancer; PIK3CA altered or wild type (wt)	Efficacy and safety	Combination: alpelisib 300, 350, or 400 mg plus fulvestrant 500 mg	Alpelisib p.o. once daily in 28-day cycle Fulvestrant i.m. on Days 1 and 15 of Cycle 1 and on Day 1 (± 3 days) of every cycle thereafter	87 PIK3CA altered[c]: 52 PIK3CA wt: 33
X1101 [b] Phase I 25-Nov-2015 Completed	Adult subjects with advanced solid malignancies and documented genetic alteration of the PIK3CA gene	Safety	Single agent: alpelisib	Alpelisib p.o. once daily: escalation part: 90, 180, 270, 350, 400 mg expansion part: 350 mg	33 (including 4 subjects with breast cancer)

AI aromatase inhibitor, HER2 human epidermal growth factor receptor-2, HR hormone receptor, i.m. intramuscular, PI3K phosphatidylinositol-3-kinase, p.o. oral, wt wild-type

[a] 30-day safety follow-up
[b] 28-day safety follow-up except in the case of death, loss to follow up, or withdrawal of consent
[c] As confirmed by the central laboratory; PIK3CA status was unknown for 2 subjects

Table 15: Overview of studies in patients with cancer or healthy subjects with PK or clinical pharmacology component

Study Code	Study objective / population	No. of treated subjects	Formulation	Dose / Regimen & Food Status
Biopharmaceutical studies				
Study A2103 (Food effect & ranitidine DDI)	Single-center, open-label, randomized, five period, ten sequence crossover study to investigate the singular and joint effect of food and the histamine H2-receptor antagonist ranitidine on the PK of oral alpelisib in healthy subjects	21	Formulation D	SD 300 mg Fasted & fed
Study X1101 (Food effect)	Exploratory, randomized, 2 period, 2 sequence crossover food effect expansion/ Japanese subjects with advanced solid tumors whose tumors have an alteration of the PIK3CA gene	8 (6 completed)	Formulation B/C	RD 350 mg Fasted & fed
Mass balance (hADME)				
Study X2107 (hADME)	Single-center, open-label study to investigate the Absorption, Distribution, Metabolism and Excretion (ADME) of alpelisib in healthy subjects	4	Radiolabeled drug in hard gelatin capsule	SD 400 mg Fasted
Special populations study				
Study A2105 (Hepatic Impairment)	Hepatic Impairment in subjects with moderate and severe impairment (based on Child-Pugh)	**Total: 23** Hepatic impairment subjects: 6 each + matching healthy subjects	Formulation D	SD 300 mg Fasted
Drug-drug interaction studies				
Study Z2102 (Everolimus DDI)	Phase I, open label safety and tolerability study of the combination of alpelisib and everolimus (and exemestane) in subjects with advanced solid tumors (Alpelisib as a potential perpetrator of a CYP3A4 drug-drug interaction)	**Total: 79 DDI assessment group:** 25 subjects dosed with everolimus and alpelisib 250 or 300 mg	Formulation D	RD 250 or 300 mg q.d. Fed

Study Code	Study objective / population	No. of treated subjects	Formulation	Dose / Regimen & Food Status
Single agent PK studies in subjects with solid cancers				
Study X2101 (First-in-human)	Phase Ia, multicenter, open-label dose escalation study of oral alpelisib in adult subjects with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene	134 single agent in solid tumors	Formulation A, B, and C	RD 30-450 mg q.d. & 120-200 mg b.i.d. Fed
Study X1101	Phase IA dose-escalation study of alpelisib in Japanese subjects with advanced solid tumors	25	Formulation B and C	RD 90-400 mg q.d. Fed
Combination PK studies with fulvestrant in subjects with advanced breast cancer				
Study X2101	Phase Ia expansion arm in combination with fulvestrant in HR+, HER2- aBC after multiple lines of therapy	87	Formulation A, B, and C	RD 300, 350, 400 mg q.d. Fed
Study C2301 (SOLAR-1)	Phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR+, HER2- aBC which progressed on or after aromatase inhibitor treatment	572	Formulation D	RD 300 mg q.d. Fed

SD: single dose administration; RD: repeated dose administration; aBC: advanced breast cancer, HR+: hormone-receptor positive; HER2-: human epidermal growth factor receptor 2 negative; HFHC: high fat high calorie; LFLC: low fat low calorie; b.i.d: twice a day; DDI: drug-drug interaction; q.d: once daily;

2.4.2. Pharmacokinetics

Analytical methods

The concentrations of alpelisib (BYL719) and its primary metabolite (BZG791) in human K_3EDTA plasma were measured using LC-MS/MS method over the calibration range of 1.00 to 1000 ng/mL. In addition, alpelisib was measured with a higher validated range from 5.00 to 5000 ng/mL and was validated in Li-Heparin as anticoagulant.

The bioanalytical methods consist of protein precipitation and analysis of the reconstituted sample by LC-MS/MS in Multiple Reaction Monitoring mode using Electron Spray Ionization as the ionization technique.

A total of seven methods were developed, validated and used throughout the clinical development of alpelisib.

Because different methods were used to measure the concentration of alpelisib, several cross-validations between methods were performed. Based on the results, all validated analytical methods can be used for quantitative determination of BYL719 in human plasma samples.

Pharmacokinetic data analysis

As subjects in the three healthy subject studies were exposed to different formulations (capsule formulation in the mass balance study), food conditions (fasted vs. fed), and/or co-administrations (acid reducing agents), no healthy subject data were pooled.

Data from patients with cancer (simplified as "Phase I pool") were pooled from single agent Phase I Study X2101 and Study X1101 for PK characterization, population PK analysis, and exposure-response analysis. Only single agent data or combination data with fulvestrant that reflected the recommended dosing regimen and conditions of administration, i.e. once daily regimen under fed conditions, were included in the pooled dataset. The Phase I pool was analysed separately from Study C2301 Phase III data given the difference in the indication, study population (line of therapy), and treatment (majority of Phase I cancer subjects received monotherapy as well as limited number of cancer subjects who received combination at the 300 mg).

Based on the Phase 1 model, another Pop PK model was developed to describe alpelisib PK in the Phase 3 study SOLAR-1, where alpelisib were co-administered with fulvestrant. The final Phase 3 model included only statistically significant covariates for weight and age.

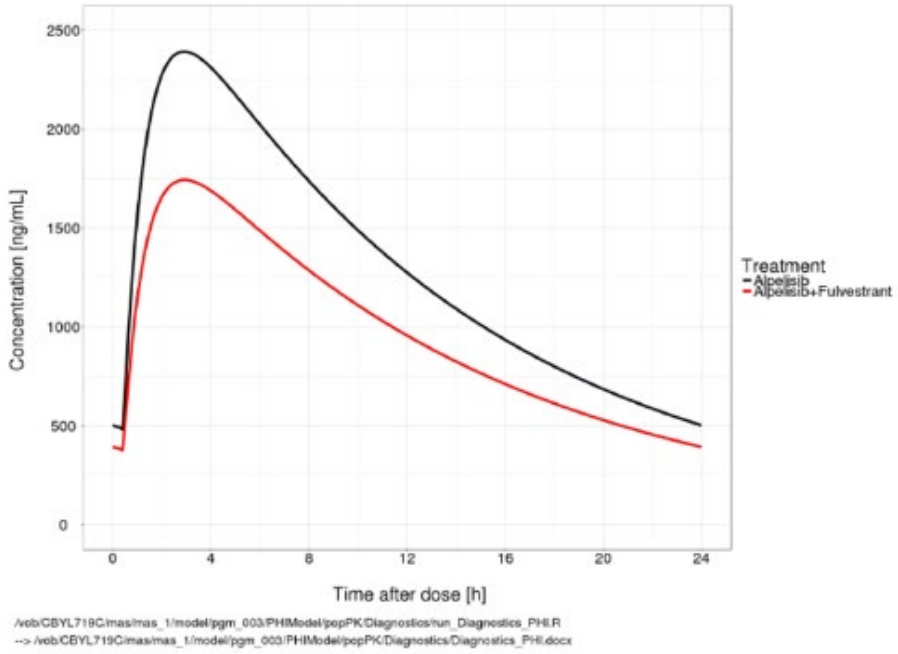


Figure 4: Predicted steady state concentration profile for alpelisib 300 mg QD under treatment with alpelisib or alpelisib + fulvestrant

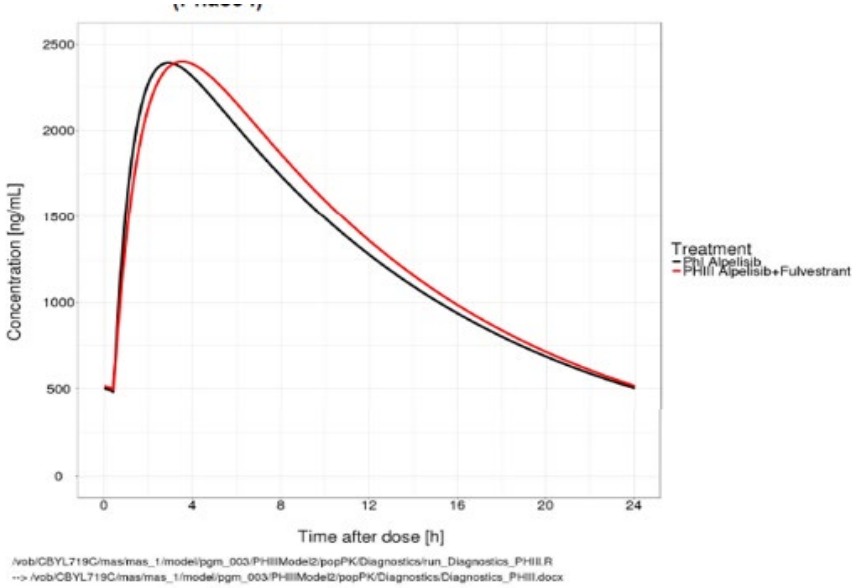


Figure 5: Predicted steady state alpelisib concentration profile at steady state under 300 mg alpelisib + fulvestrant (phase III) and 300 mg alpelisib (Phase I)

A PBPK model for alpelisib was built in GastroPlus encompassing the advanced compartment and transit absorption model linked to patient and healthy subject PK for prediction of food effect, effect of ranitidine and investigating the absorption kinetics of alpelisib. Sensitivity analysis showed that pH in the stomach and intestines have major impact on alpelisib absorption which seems to be limited by solubility. Absorption was increased in presence of food due to excretion of bile salts and decreased in presence of pH-altering agents.

The following doses were selected for evaluating absorption kinetics of alpelisib: 300 mg Formulation B/C, light meal - cancer patients with advanced solid malignancies (a) and 300 mg Formulation D light meal – healthy subjects (b). Two different dissolution models were used: Johnson for Formulation B/C and Takano for Formulation D.

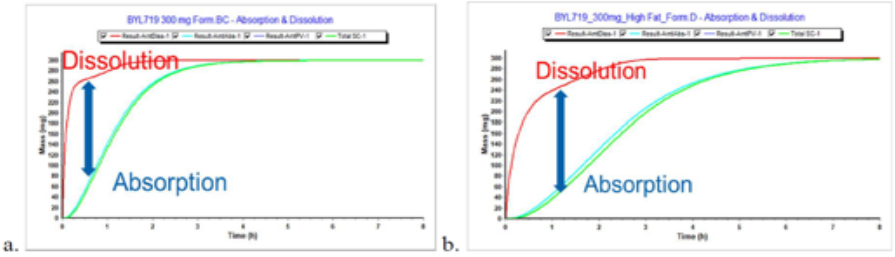


Figure 6 and Figure 7: Absorption kinetics of alpelisib when fed – diagnostic plots

The following dose was selected for evaluating absorption kinetics of alpelisib: 300 mg Formulation D (healthy subjects).

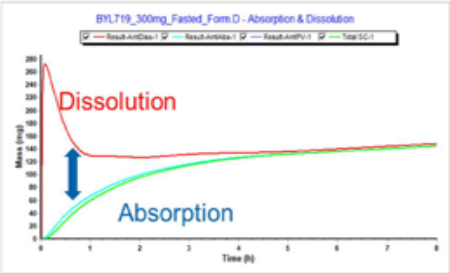


Figure 8 and Figure 9: Absorption kinetics of alpelisib when fasted – diagnostic plots

Linear mixed models were used to describe the relationship between change in QTcP, QTcF or HR to alpelisib concentration with or without fulvestrant.

Absorption

Bioavailability

No bioavailability study in humans was performed which is acceptable (see discussion on clinical pharmacology). The oral absorption and bioavailability of alpelisib was characterised using data from other clinical and non-clinical studies and supported by a GastroPlus absorption model.

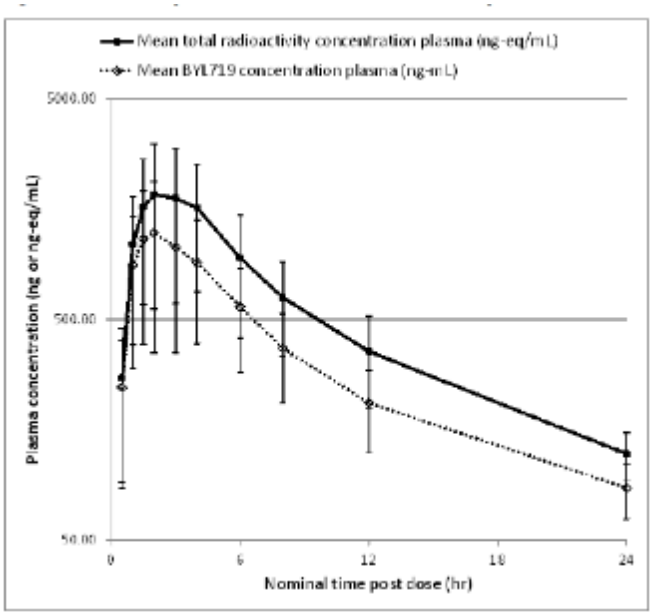
Oral bioavailability in non-clinical species was moderate (~57%) in rats after suspension dosing and complete (≥ 100%) in mice and dogs after a single dose of alpelisib as a solution. Absorption of 14C alpelisib and/or metabolites was 63% in the rat ADME, indicating that absorption is a good measure of oral bioavailability.

Absorption in humans under fasted conditions was assessed in the human mass balance Study X2107. Following oral administration of alpelisib, median time to reach peak plasma concentration (T_{max}) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen. Based on the recovery of the radioactivity in urine and the radioactivity assigned to metabolites in faeces, the absorption of alpelisib was at least 53.5% in the fasted state after a 400 mg single dose. This is in line with PBPK simulations that showed a predicted fraction absorbed of a single dose of 400 mg of alpelisib under fasted conditions was 60.7%. The observed magnitude of the food effect, however, indicates that absorption after a meal in the fed state is very high.

Based on PBPK absorption modelling, in the absence of an absolute bioavailability study, absorption was estimated to be very high (>99%) under fed condition but lower under fasted conditions (~68.7% at a 300 mg dose). Steady-state plasma levels of alpelisib after daily dosing can be expected to be reached on day 3 following onset of therapy in most patients (see SmPC section 5.2).

Based on the preclinical results suggesting a limited first path effect as well as data from the human mass balance study, the absolute bioavailability is expected to be moderate to high depending on the food status, close to the absorption fraction.

The ADME study showed that alpelisib was almost equally distributed in plasma and blood. Furthermore, the data indicated that there was no accumulation of metabolites, as the total radioactivity declined in parallel with the radioactivity attributed to alpelisib (Figure 10).



Source: [Figure 8-1] of [DMPK-RCBYL719X2107d]

Figure 10: Mean plasma 14C and BYL719 concentration time-profiles

Bioequivalence

Based on the interim CSR of Study A2109, bioequivalence was demonstrated between Formulation D (clinical formulation) and Formulation E (commercial formulation) at the highest tablet strength of alpelisib (200 mg) in both the fed state (Cohort 1, full results submitted) and the fasted state (Cohort 2, interim results submitted). The point estimates of the geometric mean ratios between formulations D and E in fed or in fasted state and the corresponding 90% CI of alpelisib exposure metrics were all within the predefined bioequivalence boundary (0.80, 1.25). In the fed state, the inter- and intra-subject variability was low with a CV% of 9.9% for AUCinf, 10.3% for AUClast, and 18.7% for Cmax (N=24).

Table 16: Statistical analysis of primary PK parameters for alpelisib for Cohort 1 (fed) (Pharmacokinetic analysis set)

					Treatment comparison 90% CI		
PK parameter (unit)	**Treatment**	**n***	**Adjusted geo-mean**	**Comparison**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf (ng*hr/mL)	A	23	9170				
	B	23	9050	B / A	0.987	0.9386	1.0375
AUClast (ng*hr/mL)	A	24	8950				
	B	24	8880	B / A	0.993	0.9436	1.0453
Cmax (ng/mL)	A	24	1340				
	B	24	1260	B / A	0.939	0.8563	1.0298
Tmax (hr)	A	24	2.50				
	B	24	3.00	B - A	0	-4.02	4.00

Treatment A = alpelisib Formulation D 200 mg in fed state; Treatment B = alpelisib Formulation E 200 mg in fed state.
Model is an ANOVA model of the log-transformed PK parameters. Included in the model were treatment, sequence, period and subjects nested within sequences as fixed effect. The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n* = number of observations used for the analysis.
For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.
Source: [A2109 – Interim CSR Table 14.2-1a]

Table 17: Statistical analysis of primary PK parameters for alpelisib for Cohort 2 (fasted) (Pharmacokinetic analysis set)

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison	Treatment comparison Geo-mean ratio	90% CI Lower	90% CI Upper
AUCinf (ng*hr/mL)	C	68	6410				
	D	68	6160	D / C	0.961	0.9098	1.0160
AUClast (ng*hr/mL)	C	71	6040				
	D	71	5780	D / C	0.957	0.9034	1.0140
Cmax (ng/mL)	C	71	725				
	D	71	675	D / C	0.932	0.8293	1.0475
Tmax (hr)	C	71	2.00				
	D	71	1.50	D - C	0	-4.00	6.88

Treatment C = alpelisib Formulation D 200 mg in fasted state; Treatment D = alpelisib Formulation E 200 mg in fasted state. Model is an ANOVA model of the log-transformed PK parameters. Included in the model were treatment, sequence, period and subjects nested within sequences as fixed effect. The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n* = number of observations used for the analysis.
For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.
Source: [A2109 –Table 14.2-1b]

The mean concentration-time profiles were slightly shifted between treatments independent of food status. This had no effect on exposure. The median Tmax was 2.5 h for formulation D and 3 h for formulation E in the fed state.

Data from food-interaction studies

Food effect was studied in 2 studies: A2103 and X1101. The data from both the formal single-dose food effect study (Study A2103) as well as the exploratory steady-state food effect expansion arm conducted in Japanese subjects with cancer (Study X1101) showed that exposure (AUCinf) is significantly increased when alpelisib is administered after a meal (see Table 18).

Table 18: Summary of statistical analysis of dose-normalized AUClast, AUC0-24 and Cmax by food condition (study X1101)

PK parameter (unit)	Treatment	n[1]	Adjusted geo-mean	Comparison(s)	Food effect comparison Geo-mean ratio	90% CI Lower	90% CI Upper
AUC0-24 (h*ng/mL/ mg dose)	Fasted	5	72.1				
	Fed	5	113	Fed : Fasted	1.56	1.02	2.39
AUClast (h*ng/mL/ mg dose)	Fasted	6	67.8				
	Fed	6	105	Fed : Fasted	1.55	1.06	2.28
Cmax (ng/mL/ mg dose)	Fasted	6	5.40				
	Fed	6	9.62	Fed : Fasted	1.78	1.13	2.79

[1] number of subjects with non-missing values
All data are divided by the actual dose.

In study A2103, in healthy volunteers after a single 300 mg oral dose of alpelisib, compared to the fasted state, a high-fat high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased AUC_{inf} by 73% and C_{max} by 84%, and a LFLC meal (334 calories with 8.7 g of fat) increased AUC_{inf} by 77% and C_{max} by 145%. No significant difference was found for AUC_{inf} between LFLC and HFHC with a geometric

mean ratio of 0.978 (CI: 0.876, 1.09), showing that neither fat content nor overall calorific intake has a considerable impact on absorption.

Alpelisib was administered concomitantly with ranitidine, a H2-receptor antagonist, with a low fat low calorie meal in study A2103 (see section on interaction studies). Under fasted condition, ranitidine co-administered two hours prior to alpelisib administration led to a reduction of both AUCinf and Cmax, by approximately 30% and 51%, respectively, and 0.48 hours median delay in Tmax compared to alpelisib alone in fasted condition. In the fed condition (LFLC), ranitidine co-administration led to a reduction of both AUCinf and Cmax, by approximately 21% and 36%, respectively, and 0.47 hours median delay in Tmax compared to alpelisib alone in fasted condition.

Distribution

Alpelisib moderately binds to protein with a free fraction of 10.8% regardless of concentration. Alpelisib was equally distributed between red blood cells and plasma with a mean *in vivo* blood to plasma ratio of 1.03. As alpelisib is a substrate of human efflux transporters, penetration of the blood brain barrier is not expected to occur in humans. The volume of distribution of alpelisib at steady state (Vss/F) is estimated at 114 litres (intersubject CV% 46%) (see SmPC section 5.2).

Elimination

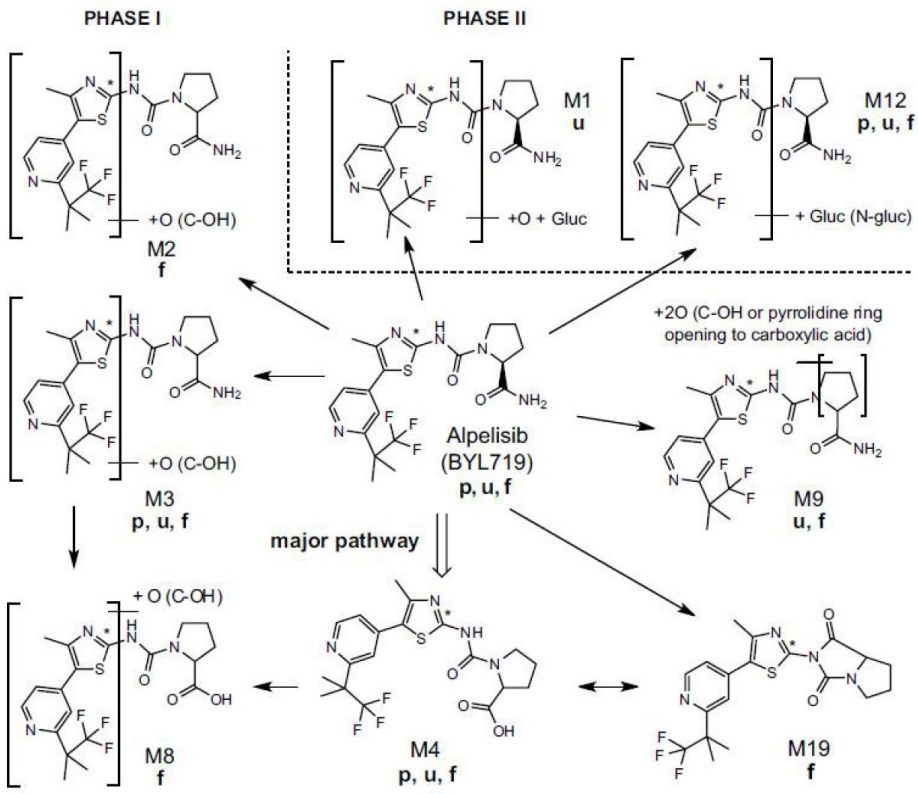
Alpelisib exhibits low clearance with 9.2 l/h (CV% 21%) based on population pharmacokinetic analysis under fed conditions. The population derived half-life, independent of dose and time, was 8 to 9 hours at steady state with 300 mg once daily.

Excretion

In a human mass-balance study, after oral administration, alpelisib and its metabolites were excreted in the faeces (81.0%), mainly through hepatobiliary export and/or intestinal secretion of alpelisib, or metabolised to BZG791. Excretion in the urine is minor (13.5%), with unchanged alpelisib (2%). Following a single oral dose of [14C]-alpelisib, 94.5% of the total administered radioactive dose was recovered within 8 days.

Metabolism

In vitro studies demonstrated that formation of the hydrolysis metabolite BZG791 by chemical and enzymatic amide hydrolysis was a major metabolic pathway, followed by minor contribution of CYP3A4. The overall contribution of CYP3A-mediatived oxidative metabolism is low with an estimated fraction metabolized (fm CYP3A4) of ~12%. Contribution of glucuronidation was negligible with overall liver-mediated metabolism (CYP mediated Phase I and Phase II metabolism together) contributing to ≤ 15% of the elimination. Alpelisib hydrolysis occurs systemically by both chemical decomposition and enzymatic hydrolysis via ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) not limited to the liver. CYP3A4-mediated metabolites and glucuronides amounted to ~15% of the dose; BZG791 accounted for ~40-45% of the dose. The rest of the absorbed fraction of the dose was excreted as alpelisib.



* Position of ^{14}C-radiolabel. f - feces, p - plasma, u - urine
Source: James et al 2015

Figure 11: Biotransformation pathways of alpelisib in healthy human subjects

Pharmacokinetics of metabolites

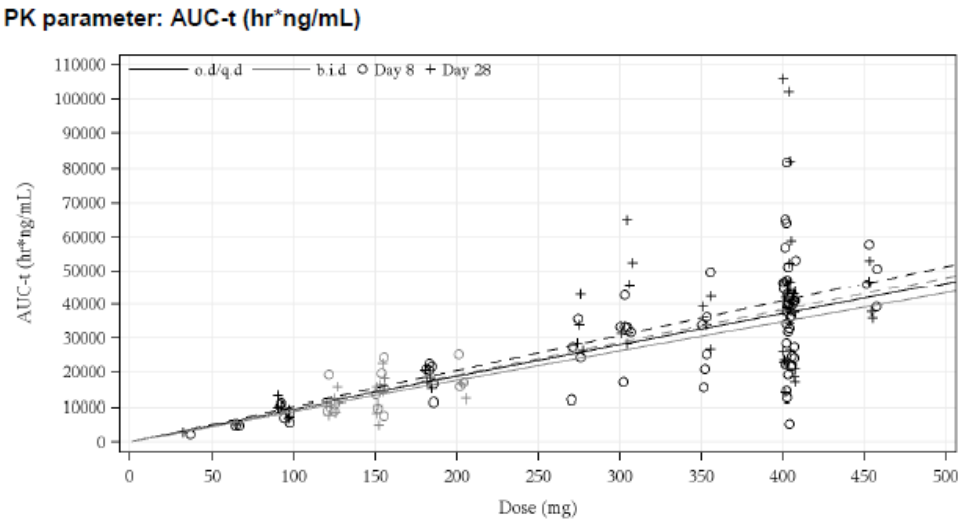
The pharmacokinetics of the pharmacologically inactive metabolite BZG791 show that it is a formation-rate limited metabolite unlikely to accumulate extensively in circulating plasma due to its short apparent half-life. Formation of BZG791 occurs by systemic metabolism via ubiquitously expressed high-capacity enzymes. As hydrolysis occurs extra-hepatically, the metabolism can compensate for the loss of liver metabolism and/or transport in severe liver impairment.

Genetic polymorphism

No studies investigating the impact of genetic polymorphism on PK were provided which is acceptable (see discussion on clinical pharmacology).

Dose Proportionality and Time-dependency

The pharmacokinetics were found to be linear with respect to dose and time under fed conditions between 30 and 450 mg. After multiple doses, alpelisib exposure (AUC) at steady state is only slightly higher than that of a single dose, with an average accumulation of 1.3 to 1.5 with a daily dosing regimen.



Model log(BYL719 parameter)=a+ß log(BYL719 dose) + patient + error
Patient effect is random
The reference dashed line is from the model and forcing the slope to 1
Source: Table 14.2-2.4

Figure 12: Dose proportionality for daily (qd and bid) single agent BYL719 AUC0-t and Cmax at steady state - FAS

Intra- and inter individual variability

The inter- and intra-subject variability were higher in cancer subjects (CV% 32.8 to 46.8 %) than in healthy subjects and were also higher in patients treated concomitantly with fulvestrant (23%-56.9%) than with alpelisib alone. In the fasted state in healthy subject, the inter-subject variability was higher than when alpelisib was taken with food.

Pharmacokinetics in target population

Pharmacokinetic data from Phase I trials Study X1101 and Study X2101 was used for population PK modelling to characterise the pharmacokinetics of alpelisib when administered as a single agent and in combination with fulvestrant and to obtain key exposure metrics AUC, Cmin and Cmax). The Phase I population PK model was used as a basis to analyze PK concentration data from Study C2301. However, minor adjustment to the model were made to reflect the Phase III data such as exclusion of the comparison between single agent and combination data as well as the gender effect (as only 1 male subject provided PK information). Covariate search was confined to covariates that were found significant in the Phase I model.

Final Phase I Population PK Model

As for the base model, a one-compartment model with a delayed first-order absorption and linear elimination was selected as the final model (Model 71). Inter-individual variability was implemented on KA, CL and V. The allometric parameters for CL and V were estimated lower than the fixed values of 0.75 and 1, respectively. CL was influenced by fulvestrant coadministration, gender and age, while V was influenced by fulvestrant coadministration and patients of Japanese ethnicity.

Table 19: Final model parameter estimates (Model 71)

Parameter	Estimate	%CV	Estimate (log scale)	SE (log scale)
KA [1/h]	1.07	7.4	0.066	0.074
θ_{CL} (allometry parameter)	0.34	26.8	-1.073	0.263
θ_V (allometry parameter)	0.52	28.1	-0.659	0.275
CL [L/h]	9.5	2.8	2.252	0.028
Fulvestrant on CL	1.34[1]	4.2	0.294	0.042
Male on CL	1.35[1]	5.1	0.296	0.051
Age on CL [1/y] [2]	0.994[2]	0.2	-0.006	0.002
V [L]	122.52	4.2	4.808	0.042
Fulvestrant on V	1.4[1]	6.4	0.339	0.064
Japanese on V	0.73[1]	10.3	-0.321	0.103
Lag [h]	0.43	1.1	-0.843	0.011
σ_{CL}	0.27			
σ_V	0.41			
σ_{KA}	0.98			
δ_1 [ng/mL]	1809.03			
δ_2	1.2			
$\sigma_{\in}$	0.08			
# Subjects	245			
# Observations	6987			
Log Lik.	-53709.9			

[1] Meaning of Coefficients (for example, CL for Fulvestrant =1.34 x 9.5=12.7 [L/h])
[2] Coefficient for 1 year older (to calculate for 10 years older use $(0.994)^{10}$=0.94)
Source:
"/vob/CBYL719C/mas/mas_1/model/pgm_003/PHIModel/popPK/Diagnostics/run_Diagnostics_PHI.R
--> /vob/CBYL719C/mas/mas_1/model/pgm_003/PHIModel/popPK/Diagnostics/Diagnostics_PHI.docx

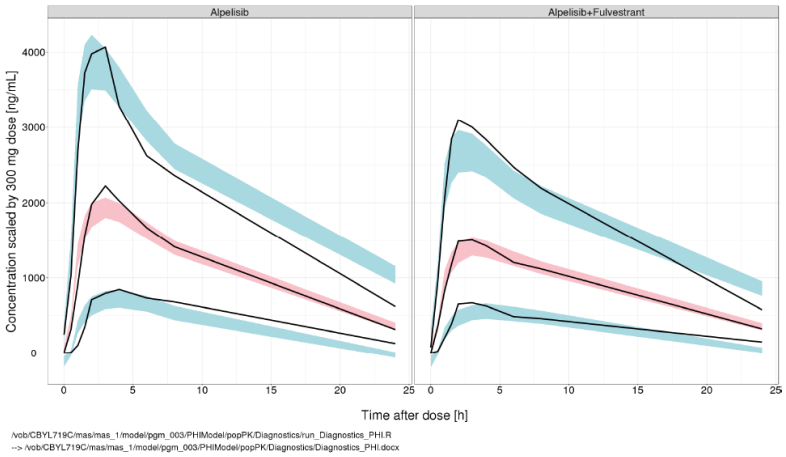


Figure 13: Visual predictive check (VPC) of the full model (71)

Final Phase III Population PK model

Similar to the Phase I model, a one-compartment model with a delayed first-order absorption and linear elimination was selected as the final model for SOLAR-1 (Model 11). Inter-individual variability was implemented on CL and V. The allometric parameter for CL was estimated to be slightly higher than that in Phase I, while the allometric parameters for V was the same.

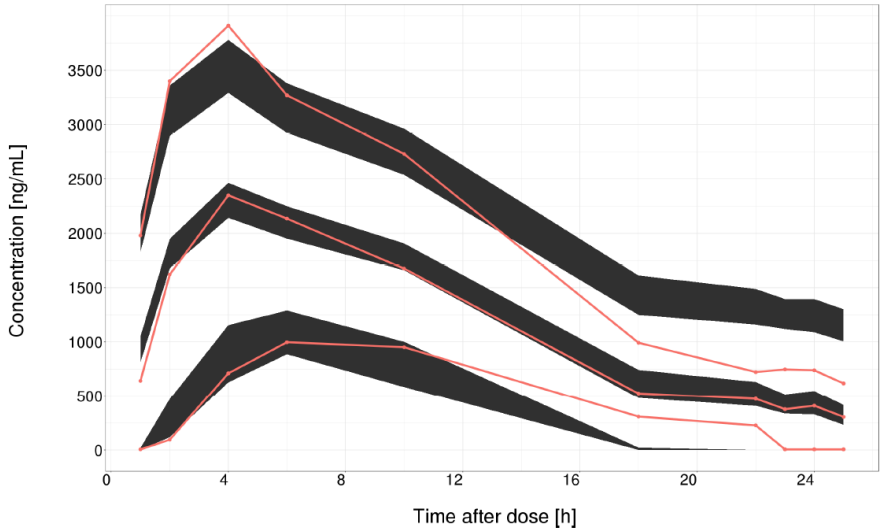
Beside the effect of body weight, age was the only covariate in the model; influencing CL in a similar manner to that of Phase I. Effects of ethnicity (Japanese or Hispanics) were found to be not significant

and thus were not kept in the final model. There was no evidence of effects due to renal or hepatic impairment, or due to acid reducing agents.

Table 20: Final model parameter estimates (Model 11)

Parameter	Estimate	%CV	Estimate (log scale)	SE (log scale)
KA [1/h]	0.75	5.5	-0.284	0.055
θ_{CL} (allometry parameter)	0.63	16.1	-0.467	0.16
θ_V (allometry parameter)	0.52	Fixed	-0.659	Fixed
CL [L/h]	9.18	2.3	2.217	0.023
Age on CL [1/y] [1]	0.995[1]	0.2	-0.005	0.002
V [L]	113.88	4.8	4.735	0.048
Lag [h]	0.43	Fixed	-0.843	Fixed
σ_{CL}	0.21			
σ_V	0.46			
σ_ϵ	518			
# Subjects	271			
# Observations	1487			
Log Lik.	-11588			

[1] Coefficient for age effect is computed as exp(Estimate(log scale)). Estimate for effect of 10 years older use $(0.995)^{10}$=0.95)
Source: "/vob/CBYL719C/mas/mas_1/model/pgm_003/PHIIIModel2/popPK/Diagnostics/run_Diagnostics_PHIII.R --> /vob/CBYL719C/mas/mas_1/model/pgm_003/PHIIIModel2/popPK/Diagnostics/Diagnostics_PHIII.docx



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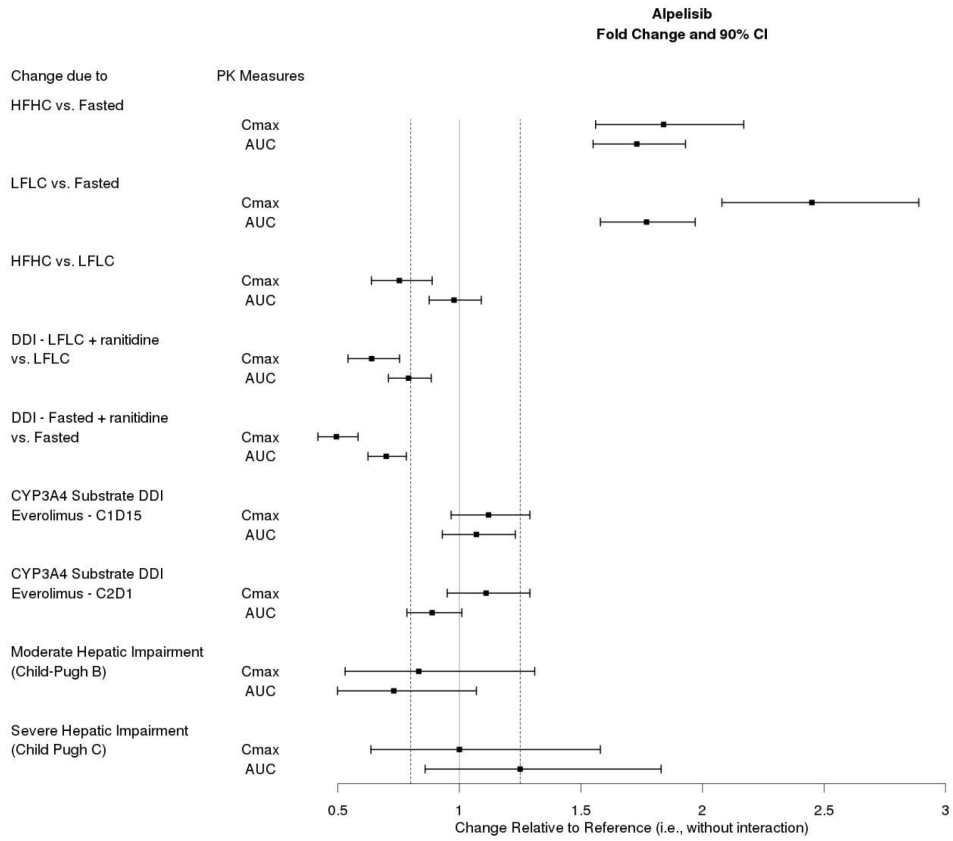
The solid lines represent the 10th, 50th and 90th percentiles of the observed concentrations. The shaded areas are the 90 % prediction intervals for the 500 simulated datasets (see Section 4.8.2 for more details).

Figure 14: Visual predictive check (VPC) of the final model (11)



Shown are adjusted geometric mean ratios and 90%CI; AUC refers to either AUCinf or AUC0-24,ss
Source: Table 2-1, Table 2-2, Table 2-4

Figure 15: Effect of intrinsic and extrinsic factors on alpelisib PK from clinical studies

Special populations

Impaired renal function

Renal impairment was assessed by means of population PK analysis based on creatinine clearance at baseline. The Phase I pharmacokinetic analysis set included 151 (61.9%) subjects with normal renal function based on creatinine clearance (CLcr ≥90 mL/min), 72 (29.5%) subjects with mild renal impairment (CLcr 60 to <90 mL/min), 20 (8.2%) subjects with moderate renal impairment (CLcr 30 to <60 mL/min) and 1 (0.4%) subject with severe renal impairment (CLcr <30 mL/min) (Phase I PopPK Report). The Phase III data sets included 117 (43.2%) cancer subjects with normal renal function, 108 (39.9%) cancer subjects with mild renal impairment, and 45 (16.6%) cancer subjects with moderate renal impairment (Phase III PopPK Report). During covariate search, no evidence of an effect by the degree of renal impairment on clearance or volume was found in either analyses.

Impaired hepatic function

In study A2105, a phase 1, open-label, single-dose, multicenter, parallel group study to assess the pharmacokinetics and safety of alpelisib (BYL719) in subjects with hepatic impairment compared to matched healthy control subjects, Cmax for alpelisib decreased by approximately 17% for moderate hepatic impairment vs. healthy control group. For the severe hepatic impairment group, Cmax was comparable relative to the healthy control group. AUClast for alpelisib decreased by approximately 27% for moderate hepatic impairment vs. healthy control group. For the severe hepatic impairment group, AUClast was 26% higher compared with the healthy control group. Values of AUCinf were

similar to those of AUClast across hepatic groups. Cmax for the metabolite, BZG791, was comparable in moderate hepatic impairment vs. healthy control group. For the severe hepatic impairment group, Cmax increased by 74%. AUClast for BZG791 decreased by approximately 12% for moderate hepatic impairment vs. healthy control group. It increased by 145% for severe hepatic impairment vs. healthy control group. Values of AUCinf were similar to those of AUClast across hepatic groups. The metabolic ratio of BZG791 was also increased (geometric mean of 0.472 [range: 0.323 to 0.580]) in subjects with severe hepatic impairment compared with subjects in the healthy control and moderate hepatic impairment group.

Gender

The impact of gender on the pharmacokinetics of alpelisib was evaluated with a population PK approach. Due to pivotal Study C2301 encompassing primarily females (one male was enrolled), the assessment was based on the Phase I population PK model. The analysis included 52 (21.2%) males and 193 (78.8%) females from studies X1101 and X2101 single agent and fulvestrant combination data. In the final model, males had a 35% higher clearance (CL) compared to females, leading to a reduction in AUC by 25% compared to a female with the same covariates.

Race

The impact of ethnicity was assessed by population means in the Phase I pool and Phase III data.

The Phase I data set included 25 subjects (10%) of Japanese ethnicity. The model estimated that Japanese subjects had a lower total volume by about 27% compared to non-Japanese subjects, causing an effect on Cmin and Cmax but not AUC (since clearance is not altered). It was estimated that Cmin was lower by 35% and Cmax higher by 19%. In addition, the PK parameters estimated by NCA methods and Ctrough summarized from the Phase I pool for monotherapy were formally compared for Japanese and non-Japanese by dose level and visit. While there was a trend towards a greater exposure (particular for Cmax), smaller Ctrough and shorter elimination half-life based on geometric mean and median values for Japanese vs. non-Japanese subjects, the magnitude of changes were not significant across PK parameters.

The impact of ethnicity found in the Phase I popPK analysis was tested in the Phase III population PK model and was not found to be significant.

Weight

The impact of weight on the pharmacokinetics of alpelisib was evaluated with a population PK approach. In the Phase I data set, 90% of the subjects had a baseline body weight between 49-95 kg with a population median body weight at baseline equal to 66.75 kg. The final model assessed the effect of weight on clearance and volume to be small. Compared to the typical subject weighing 66.75 kg, for a subject weighing 50 or 95 kg, CL was estimated to be lower by 9% or higher by 11%, respectively. Based on these estimates, compared to 66.75 kg, for the weight range of 50-90 kg, exposure ranges were: Cmin: +5% to -5%, Cmax: +13% to -12% and of AUC: +10% to -10%.

In the Phase III data set, 90% of the subjects had a baseline body weight between 48-98 kg with a population median body weight at baseline equal to 67.2 kg. The final model assessed the effect of weight on clearance and volume to be small. Compared to the typical subject weighing 67 kg, for a subject weighing 50 or 90 kg, CL was estimated to be lower by 17% or higher by 20%, respectively. Volume was estimated to be lower by 14% or higher by 16%, respectively. Based on these estimates, compared to 67 kg, for the weight range of 50-90 kg, exposure ranges were: Cmin: +24% to -20%, Cmax: +18% to -16% and of AUC: +20% to -17%.

Elderly

The effect of age was assessed by population mean PK parameter values from the Phase I pool and Phase III data. The Phase I data set included subjects with baseline age ranging from 21 to 82 years for a median of 58 years (90% range: 39-76). Based on the final model age decreased CL by only 6% for subjects 10 years older than average with no effect on volume. Thus, a 78-year-old subject was estimated to have a lower CL (or higher AUC) of about 12%. In addition, the PK parameters estimated by NCA methods and Ctrough summaries in the Phase I pool were formally compared based on age categories (<65 years or ≥ 65 years) by dose level and visit for monotherapy and in combination with fulvestrant. The results showed no significant difference on PK parameters or Ctrough for either monotherapy or combinations, respectively, based on geometric mean and median values. The Phase III data set included subjects with baseline age ranging from 25 to 87 years for a median of 62 years (90% range: 46-79). Based on the final model age decreased CL by 5% for subjects 10 years older than average with no effect on volume.

Table 21 displays the number of subjects included in the popPK datasets (N) for each age group.

Table 21: Number of subjects by age groups

PK Trials	Age 65-74 (N/total number)	Age 75-84 (N/total number)	Age 85+ (N/total number)
X1101	5/25	1/25	0/25
X2101	44/220	13/220	0/220
C2301	79/245	31/245	1/245

Pharmacokinetic interaction studies

In silico

Effect of CYP3A4 inhibitors or inducers on the Pharmacokinetics of Alpelisib

CYP3A4 is the predominant enzyme involved in the metabolism of alpelisib, however the overall contribution of CYP3A metabolism was considered low with an estimated fraction metabolized (fm) of 12%. The fm via CYP3A4 of 0.12 was established based on the oxidative metabolites identified in the human ADME study (CBYL719X2107).

Based on a PBPK model for alpelisib created with the SimCYP software simulations with the strong CYP3A4 inhibitor ritonavir and strong CYP3A4 inducer rifampin were conducted in lieu of a clinical study to assess the risk of an interaction. An exposure change at steady-state in terms of AUC was predicted as 1.16-fold [1.11; 1.21] and 0.84-fold [0.80; 0.87] with an oral administration of alpelisib at MTD (400 mg once daily) in the presence of ritonavir (100 mg b.i.d) and rifampicin (600 mg once daily), respectively.

Model sensitivity of fraction metabolized by CYP3A4 (fm CYP3A4) for alpelisib was investigated in the range between 0.125 and 0.207. The highest observed changes of alpelisib AUC were observed for the highest investigated fm, CYP3A4 of 0.207 with simulated AUC ratios of 1.27 with ritonavir and 0.75 with rifampicin.

Effect of alpelisib on the Pharmacokinetics of CYP2C9 substrates with narrow therapeutic window

As alpelisib led to a concentration-dependent induction of CYP2C9 in vitro, PBPK simulations were carried out to assess the *in vivo* risk of an interaction with a CYP2C9 substrate, with a narrow

therapeutic window index, in lieu of a clinical study. After co-administration of alpelisib (300 mg p.o., once daily for 20 days), AUC and Cmax ratios of warfarin (10 mg p.o., single dose at day 8) were estimated to be 0.91 and 0.99, respectively, indicating little to no induction potential of alpelisib on CYP2C9 (see Table 22).

The PBPK modeling platform was not fully validated to predict the induction potential on CYP2C9 due to lack of clinical reference data. A sensitivity analysis on the CYP2C9 induction parameters IndC50 (range: 0.1 – 20 µM) and Indmax (range: 1 – 20) showed a maximal warfarin (10 mg) AUC change of 0.2 when co-administered with alpelisib (300 mg).

Effect of alpelisib on the Pharmacokinetics of CYP3A4 substrates

DDI simulation was performed to explore the effect of alpelisib on the everolimus PK at steady-state (Table 22). No or only slight increase of everolimus AUC and Cmax at the last dose after oral administration of 2.5 mg q.d. for 15 days was predicted with co-administration of alpelisib (250 and 300 mg p.o., q.d. for 15 days) (see Table 22).

Table 22: Simulated DDI effects of alpelisib on the systemic exposures of everolimus and warfarin

Victim	Day	Inhibition	N	Cmax (ng/mL) Predicted	AUC(0-24h) (ng·h/mL) Predicted	Cmaxi/Cmax Predicted	AUCi/AUC Predicted
Everolimus (2.5 mg), multiple dose, p.o., q.d.	15	Without inhibitor	100	9.04 (10.3) **Observed:** 5.8 [1]	57.1 (28.7) **Observed:** 34 [1]	-	-
		+ alpelisib (250 mg, multiple dose, p.o., q.d. for 15 days)		9.92 (12.4) 4.54 (0.74-62.8) [2] **Observed:** 6.0 (3.75-13.3) [2, 3]	70.2 (53.0) 59.4 (6.93 - 329) [2] **Observed:** 50 (27.4-148) [2, 3]	1.09 (0.36) 1.04 (0.43-2.27)[2]	1.23 (0.64) 1.07 (0.35 – 4.03)[2]
		+ alpelisib (300 mg, multiple dose, p.o., q.d. for 15 days)		10.1 (12.7) 4.69 (0.75-64.2) [2] **Observed:** 6.1 (3.03-10.4) [2, 3]	72.6 (55.7) 59.1 (7.01-346) [2] **Observed:** 71.5 (31.7-76.1) [2, 3]	1.11 (0.38) 1.06 (0.43-2.37)[2]	1.27 (0.69) 1.11 (0.34 – 4.28)[2]
Warfarin (10 mg), single dose, p.o.	8	Without inhibitor	100	1086 (408)	41937 (31721) [4]	-	-
		+ alpelisib (300 mg, multiple dose, p.o., q.d. for 20 days)		1079 (404)	37273 (26989) [4]	0.99 (0.01)	0.91 (0.07)

Pharmacokinetic data based on plasma concentrations are represented as means with SD in parentheses; otherwise noted. Trial design parameters for the simulation were taken from Table 3-2.

1) Measured mean AUCinf and Cmax values based on blood concentrations after single oral administration of everolimus at 2 mg (Kovarik et al 2005) were converted to those on plasma concentrations using a reported B/P ratio of 2.6 (Table 6-4).

2) Median with range (if any)

3) Observed data (CBYL719Z2102). The AUC and Cmax values of everolimus on blood concentrations were measured in the presence of co-administration of alpelisib at 250 and 300 mg. These were converted to those on plasma concentrations using a reported B/P ratio of 2.6 (Table 6-4).

4) AUCinf

For midazolam, the simulated AUC and Cmax change (2 mg p.o., single dose at Day 8) with coadministration of alpelisib (400 mg p.o., q.d. for 15 days) was estimated to 1.19-fold and 1.04-fold (geometric mean), respectively. On the contrary, when applying the alpelisib model with the time-dependent inhibition only or only the induction effect on CYP3A4, the predicted midazolam AUC ratio was 6.48-fold and 0.10-fold, respectively. The predictions indicate that the TDI potential of alpelisib is balanced with a strong induction effect, resulting in a net *in vivo* DDI potential of alpelisib as a weak perpetrator.

Changes of the systemic exposures after oral administration of rifampicin (600 mg once daily), ribociclib (400 and 600 mg once daily) and ritonavir (100 and 600 mg once daily) in the absence and presence of co-administration of alpelisib (300 or 400 mg p.o., once daily) were simulated. Rifampicin and ritonavir are known as strong auto-inducer and -inhibitor of CYP3A4, respectively, whereas ribociclib is a weak auto-inhibitor of CYP3A4. The AUC and Cmax ratio of alpelisib (400 mg p.o., q.d. for 7 days) over oral administration ritonavir or rifampicin was predicted to be 1.16-fold and 1.09-fold for ritonavir and 0.84-

fold and 0.91-fold for rifampicin, respectively. Based on the Simcyp simulation, no clinical relevant effects are expected after simulations of alpelisib 300 mg qd for 7 days administered with or without ritonavir, rifampicin or ribociclib.

Effect of Alpelisib on the Pharmacokinetics of CYP2B6 substrates

Due to the difficulties with the induction predictability by PBPK modeling, only static mechanistic assessments were carried out. With sensitive CYP2B6 substrates, such as the antidepressant bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib based on this conservative assessment due to the observed induction of CYP2B6 by alpelisib *in vitro*.

In vivo

Interaction with CYP3A4 inducers (encorafenib)

The pharmacokinetics of alpelisib in the presence of increasing doses of encorafenib, a strong inducer of CYP3A4 have been assessed in a clinical Phase Ib study (NCT01719380). At 300 mg at steady state, mean Cmax were 2743 ± 520 ng/mL and AUC0-24 was 25126 ± 3513 h×ng/mL when co-administered with 200 mg encorafenib (van Geel et al 2017), which was comparable to levels of single agent.

Interaction with CYP3A4 substrate (everolimus)

Study Z2102, a phase Ib dose-finding study of alpelisib plus everolimus and alpelisib plus everolimus plus exemestane in patients with advanced solid tumors, with dose-expansion cohorts in renal cell cancer, pancreatic neuroendocrine tumors and advanced breast cancer patients investigated whether alpelisib affected everolimus PK and determined the magnitude of the drug-drug-interaction.

In the presence of alpelisib at doses of either 250 mg or 300 mg after 1 week of co-administration (Cycle 1 Day 15) and after 3 weeks of co-administration (Cycle 2 Day 1) pharmacokinetics of a 2.5 mg dose of everolimus were largely unchanged on average to those observed at Day 7. Geometric mean Cmax was 18.4 ng/ml and 19.3 ng/ml in the 250 mg alpelisib and 300 mg alpelisib treatment groups at Cycle 1 Day 15, respectively, and 18.7 ng/ml and 13.0 ng/ml at Cycle 2 Day 1. The geometric mean of AUCtau (or AUClast) was found to be comparable at Cycle 1 Day 15 with 144 ng×hr/ml and 147 ng×hr/ml in the 250 mg alpelisib and 300 mg alpelisib treatment groups, respectively, but slightly lower after 3 weeks of concomitant administration at Cycle 2 Day 1 independent of the alpelisib dose, with 110 ng×hr/ml and 108 ng×hr/ml. The concentration-time profiles of everolimus are shown in Figure 11-3 on Cycle 1 days 7 and 15 and Cycle 2 day 1.

The effect of alpelisib (as both an inducer and time–dependent inhibitor of CYP3A) on primary PK parameters for everolimus was also assessed by statistical analysis using a linear mixed effect model. For Cycle 1 Day 15 (everolimus+alpelisib), Cmax geometric mean increased by 12% compared to Cycle 1 Day 7 (everolimus alone). AUCtau geometric mean for Cycle 1 Day 15 was in the same range as Cycle 1 Day 7 and decreased by 11.2% for Cycle 2 Day 1 compared to Cycle 1 Day 7.

Interaction with acid reducing agents (ranitidine)

Study A2103, a single-center, open-label, randomized, five period, ten sequence crossover study, investigated the effects of food and the histamine H2-receptor antagonist ranitidine on the pharmacokinetics of oral alpelisib in healthy volunteers.

Co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced bioavailability of alpelisib and decreased overall exposure. In the presence of a LFLC meal, AUCinf was decreased by 21% and Cmax by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUCinf and 51% decrease in Cmax with ranitidine compared to the fasted state without co-administration of ranitidine.

Population PK analysis which assessed the intake of ARAs (H2-receptor antagonists, proton pump inhibitors and antacids) as time-varying variable on clearance and volume, found no evidence of an effect of either type of acid reducing agent under fed conditions in the Phase 1 or in the Phase 3 Pop PK population. More than half of the subjects in the Phase 1 pool took ARAs at least once during PK sampling phase, while about a third of the Phase 3 population took ARAs at least once during the duration of alpelisib treatment.

Effect of fulvestrant on the Pharmacokinetics of Alpelisib

No dose adjustments for alpelisib are recommended when co-administered with fulvestrant due to the absence of any clinically relevant DDI on alpelisib PK due to fulvestrant. Alpelisib had no effect on the PK of fulvestrant.

Based on available information on fulvestrant and an understanding of alpelisib's ADME properties, no metabolic and transporter drug-drug-interaction between the two drugs is anticipated. Also due to the difference in route of administration (oral vs. intra-muscular) an absorption-related direct interaction can be considered unlikely.

Clinical PK data of alpelisib at doses of 300 mg, 350 mg and 400 mg once daily in combination with fulvestrant were collected as part of Study X2101. Primary PK parameters such as peak levels (Cmax) and exposure (AUC0-24) were overall comparable across the different dose levels except for the 400 mg treatment group which included the majority of subjects, possibly due to increased inter-subject variability (Section 2.3.1). Phase I population PK analysis based on the Phase I pool indicated that exposure is lower by 25% in combination with fulvestrant, as compared to that of the single agent [Phase I PopPK Report]. As the Phase III population model, however, displayed similarities in alpelisib's estimates of clearance and volume to those of the single agent from Phase I population model, and thus similar overall exposure at the 300 mg dose, this suggest that there is no effect on the PK of alpelisib due to fulvestrant (Phase III PopPK Report).

Additionally, the results from Study C2301 showed that alpelisib did not have an effect on the PK of fulvestrant.

2.4.3. Pharmacodynamics

Mechanism of action

Alpelisib is an α-specific class I phosphatidylinositol3kinase (PI3Kα) inhibitor. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and AKT-signalling, cellular transformation and the generation of tumours in *in vitro* and *in vivo* models.

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets including AKT, and showed activity in cell lines harbouring a PIK3CA mutation.

In vivo, alpelisib inhibited the PI3K/AKT signalling pathway and reduced tumour growth in xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in oestrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased anti-tumour activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.

The PI3K/AKT signalling pathway is responsible for glucose homeostasis, and hyperglycaemia is an expected on-target adverse reaction of PI3K inhibition (see SmPC section 5.1).

Primary and secondary pharmacology

Study X2101

Study X2101 was a multicenter, Phase IA, dose-escalation/expansion study of oral alpelisib in adult subjects with advanced solid malignancies. In this study, monotherapy and concomitant treatment with fulvestrant was studied. There was a higher response rate, when alpelisib was combined with fulvestrant, than when treated with alpelisib alone.

Single agent alpelisib

Overall, the ORR per RECIST (Response Evaluation Criteria in Solid tumors) 1.0 was 6% (8/134 patients) based on the full analysis set (FAS); with one patient achieving a CR and seven patients having a PR. The disease control rate (DCR) was 58.2% (78/134 patients). Of the 36 patients with breast cancer, 23 had ER+/HER2- disease. No complete or partial responses were observed in the other 13 breast cancer patients. However, 2 patients with ER-/HER2- breast cancer had tumor shrinkage of -25.0% and -23.5%, and a ER+/HER2+ breast cancer patient had a tumor shrinkage of -29.6%.

One PR (4.3%) was observed among 23 study patient with ER+/HER2- breast cancer treated with BYL719 as single agent. 13 patients (56.5%) had SD as the best overall response in this population. The disease control rate in patients with ER+/HER2- breast cancer was 60.9% [38.5; 80.3].

Combination alpelisib+fulvestrant

Eighty-five patients were treated with BYL719 in combination with fulvestrant, among them 52 with ER+ breast cancer harboring an alteration of the PIK3CA gene (mutation or amplification) and 33 with PIK3CA wild type ER+ breast cancers. Most patients had ER+ HER2- breast cancer with PIK3CA alteration, 49 of those were evaluable for response. 14/49 patients with ER+/HER2- PIK3CA altered breast cancer achieved a partial tumor response during treatment; the ORR was 28.6% [95% CI 16.6, 43.3]. The disease control rate (DCR) in these patients was 79.6% [95% CI 65.7, 89.8] and the clinical benefit rate (CBR), defined as CR or PR or SD >24weeks, was 44.9% [95% CI 30.7; 59.8]. In contrast, no objective tumour responses were observed in ER+/HER2- PIK3CA wild-type breast cancer patients. The DCR in this population was 46.9% [95% CI 29.1; 65.3]. The posterior mean and 95% credible intervals of ORR for the PIK3CA mutant cohort was 26.1% [15%, 38.9%]. Further results are presented under clinical efficacy, supportive studies.

Secondary pharmacology

Serial, single post-dose ECGs (triplicate at baseline) were collected with time-matched PK samples (1h, 2h, 4h, 8h, and 24h) following a single dose (Day 1) and at steady-state (Day 8 and Day 29) to evaluate the effect of alpelisib on the QTc interval in subjects with advanced solid tumors and metastatic breast cancer as single agent and in combination with fulvestrant.

QT correction was performed using QTcF and population derived corrected QTc (QTcP). As only QTcP fully decoupled the effect of heart rate (RR) on QT intervals this correction was used in concluding on the QT effect of alpelisib. Hysteresis plots confirmed the absence of a delayed QT effect. Central tendency analysis was conducted across all dose levels, regimen and occasions for single agent and in combination. The analysis showed small increases in QTc values around Tmax across all dose levels and in single agent vs. combination with fulvestrant. QTcF values showed a similar trend as observed with QTcP across all patient cohorts. A linear mixed effect model was used to fit the relationship between delta QTcP and time matched alpelisib concentrations with patient as a random effect. A treatment effect, with or without fulvestrant, was implemented as fixed effect on both the slope and the intercept. The concentration-effect regression analysis for change in QTcP parameters are presented in Figure 16. The solid regression lines describe the linear relationship between alpelisib plasma concentration (in grey single agent and in black for combination arm) and ECG parameter

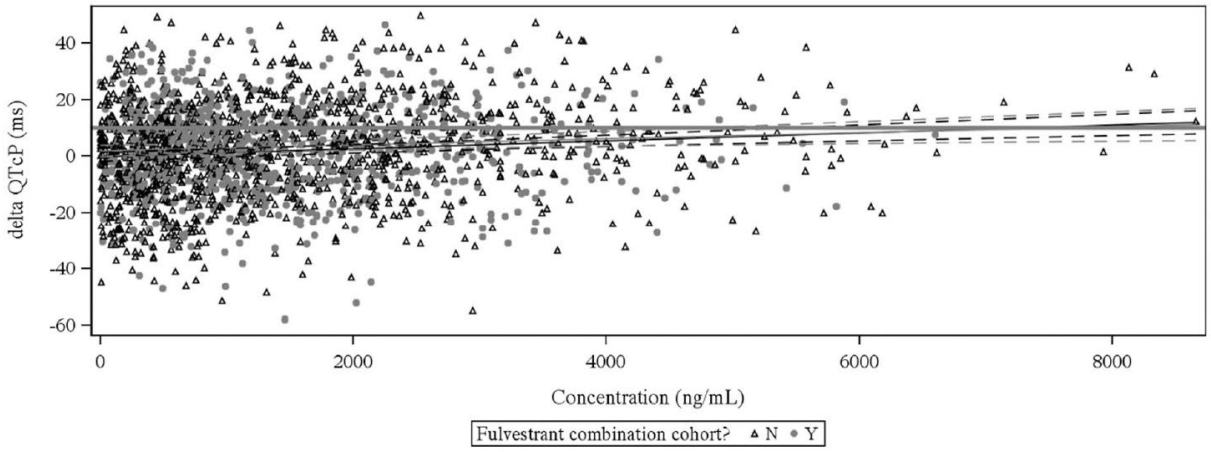
change from baseline, estimated from the linear mixed effect model. The dashed lines represent the corresponding two-sided lower and upper 90% confidence bands for the single arm group (grey lines) and the combination arm (black lines).

The analysis of the QTc interval with increasing dose did not reveal an increased risk of clinical significant QTc prolongation at the clinical relevant doses. However, the data showed a large variability in QTc change (Figure 16) .

Change from baseline for QTcF was assessed in the Alpelisib Cardiac Safety Report for Study X2101. Of the 86 subjects with post-dose measurement treated with combination therapy, 31 subjects (36%) had increased QTcF above 30 ms. Most of the cases were observed during the first treatment cycle, which is most likely due to more measurements during this period. In 25 out of the 31 subjects other reasons for QTc prolongation were identified. The most common risk factors associated with QT prolongation were hypokalemia (n=10), previous anthracycline treatment (n=6) or current hypothyroidism (n=9), ciprofloxacin treatment or diarrhea (n=5 and n=7, respectively) and ondansetron treatment (n=5 cases).

Overall, hypokalaemia was the most frequently occurring factor in common in subjects with QTc prolongation above 30 ms.

In the cardiac safety report, there was a positive association between alpelisib concentration and QTc with a slope of 0.0014 ms/ng/mL (90%CI: 0.0009; 0.0019). However, considering the therapeutic range, the geometric mean Cmax for the recommended dose of 300 mg was 2900 ng/ml, which was associated with an estimated QTcP of 4.9 ms (90% CI 2.78;7.02) and QTcF of 7.3 ms (90%CI: 5.29, 9.36).



Source: [Alpelisib Cardiac Safety Report–Figure 5-15]

Figure 16: Scatter plot of QTcP versus alpelisib concentrations (PK-QT analysis set)

Table 23: Summary of concentration-delta QTcP model for plasma alpelisib (PK-QT analysis set)

Cohort	Alpelisib Concentration (unit)	Estimate (ms)	90% CI (ms)	
			lower	Upper
Single agent administration	2900 (ng/mL)	3.8	2.14	5.46
	5470 (ng/mL)	7.4	4.81	10.01
	7000 (ng/mL)	9.6	6.26	12.86
Combination administration	2900 (ng/mL)	4.9	2.78	7.02
	4760 (ng/mL)	6.9	3.83	10.00
	7000 (ng/mL)	9.3	4.82	13.88

Source: [Alpelisib Cardiac Safety Report-Table 5-11]

Genetic differences in PD response

In patients with tumours with PIK3CA mutations there was an indication of a better response compared to patients with wild type (Figure 17).

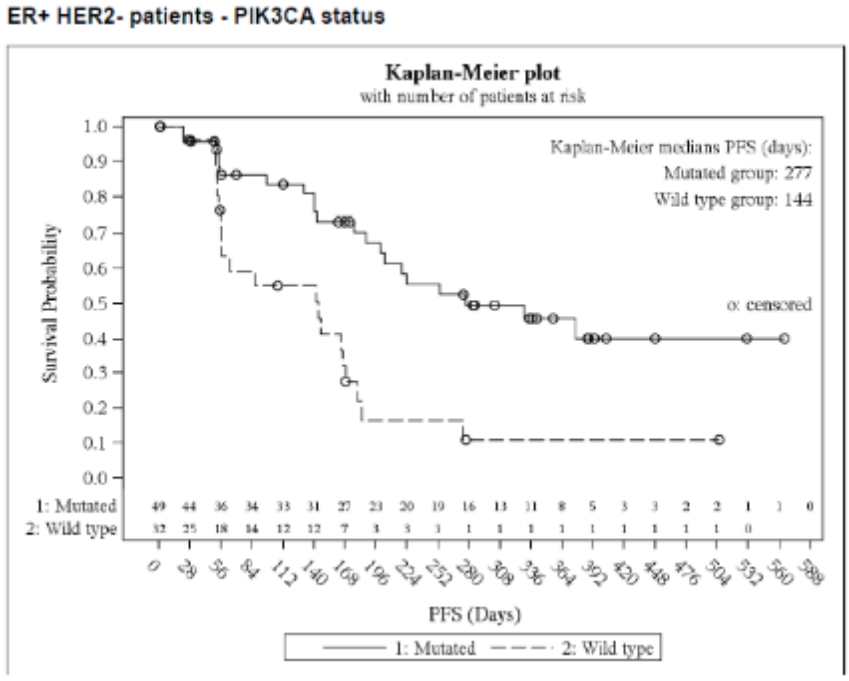


Figure 17: Kaplan-Meier plot of progression-free survival as per investigator assessment in the Breast ER+, HER2- patients treated at or less than MTD by PIK3CA alteration status – combination agent (FAS)

Relation between plasma concentration and effect

Table 24: Overview of exposure-response analyses

Analysis	Type	Response Parameters[1]	Exposure metric	Study Data[2]
Phase I exposure –response				
Cox regression	Efficacy	PFS	Time-averaged popPK predicted AUC0-24	X2101 (combination only)
Cox regression	Safety	Time to first hyperglycemia (Grade 2 or worse)	Time-averaged popPK predicted AUC0-24	X2101+ X1101
Cox regression	Safety	Time to first rash (Grade 2 or worse)	Time-averaged popPK predicted AUC0-24	X2101+ X1101
PK/QT	Safety	ECG / QTcP and QTcF	Time-matched concentrations	X2101

Analysis	Type	Response Parameters[1]	Exposure metric	Study Data[2]
Phase III exposure –response				
Cox regression	Efficacy	PFS	Time-averaged projected Ctrough	C2301
Cox regression and Kaplan-Meier plots	Efficacy	PFS	Time-averaged projected Ctrough and dose intensity as categorical variable (placebo, low exposure and high exposure)	C2301
Cox regression	Safety	Time to first hyperglycemia (Grade 2 or worse)	Time-averaged projected Ctrough and instantaneous projected concentration	C2301
Cox regression	Safety	Time to first rash (Grade 2 or worse)	Time-averaged projected Ctrough and instantaneous projected concentration	C2301

[1] as defined by adverse events of special interest (AESI) grouping of preferred terms [Study C2301 - Table 16.2.7-1.3]
[2]The analysis sets are detailed in Appendix 1-Table 3-1

Exposure-efficacy analysis

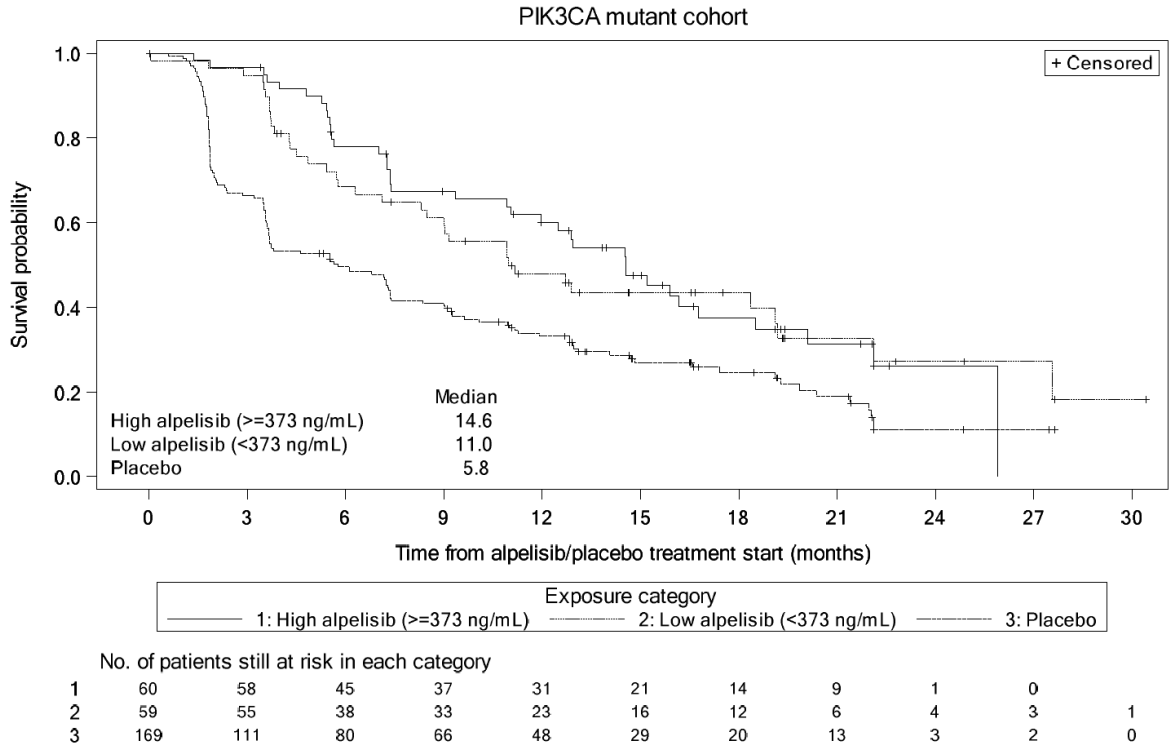
- Phase III (C2301)

PFS was analysed using an extended Cox regression model with log of time-averaged PopPK derived AUC0-24 as time-dependent covariate. The analysis was performed by PIK3CA mutation status [Study X2101]. The analysis of exposure-efficacy relationship showed a trend towards a better treatment

benefit with increasing exposure in subjects with PIK3CA mutation, though with a large variability in the hazard ratio estimate (HR=0.852; 95% CI:0.435, 1.670) for a 50% increase in AUC0-24.

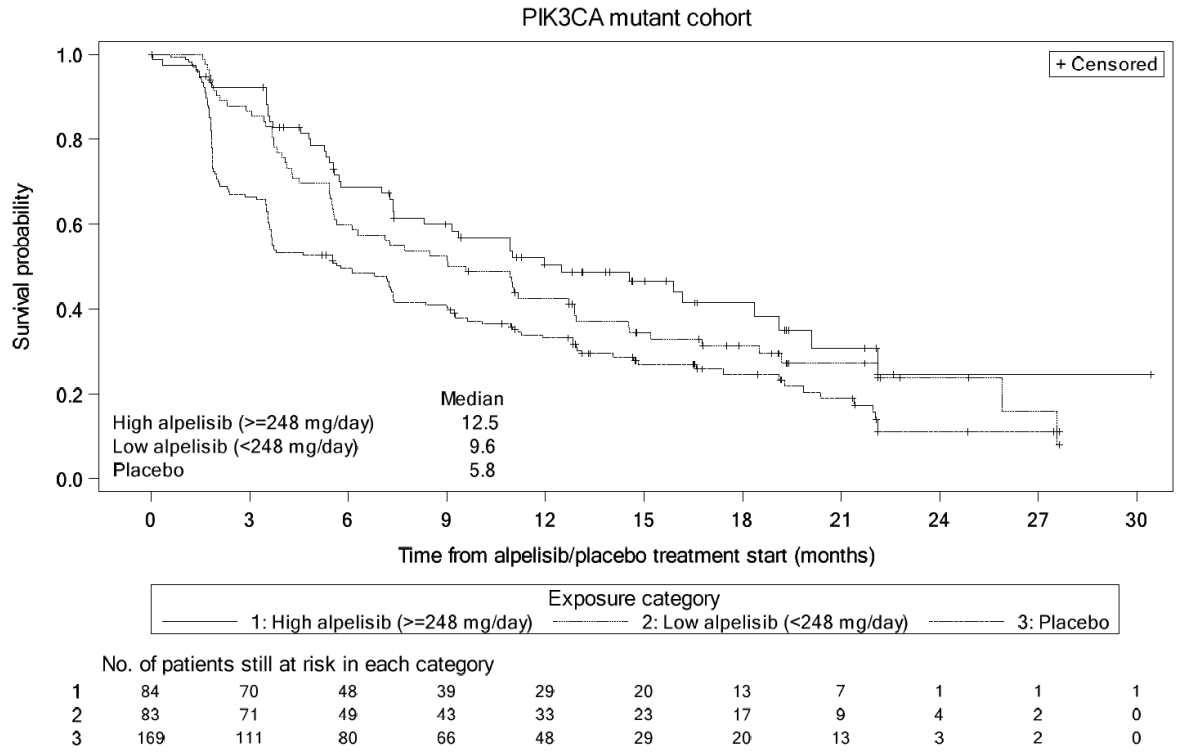
- Phase I fulvestrant combination data (Study X2101)

PFS was analysed using an extended Cox regression model with log of time normalized projected concentrations as time-dependent covariate.



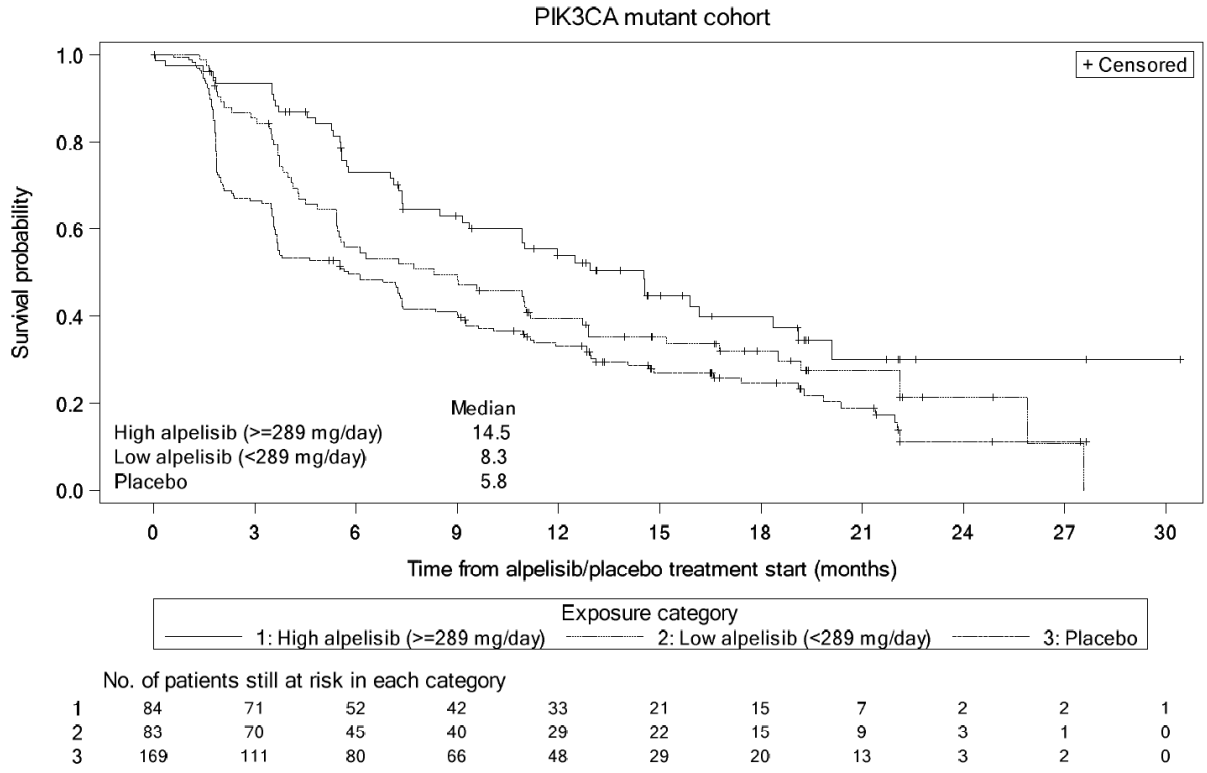
Source: Appendix 1-Figure 3-23

Figure 18: Kaplan-Meier plot of PFS by median time-normalized projected Ctrough in the PIK3CA mutant cohort – study C2301 (FAS)



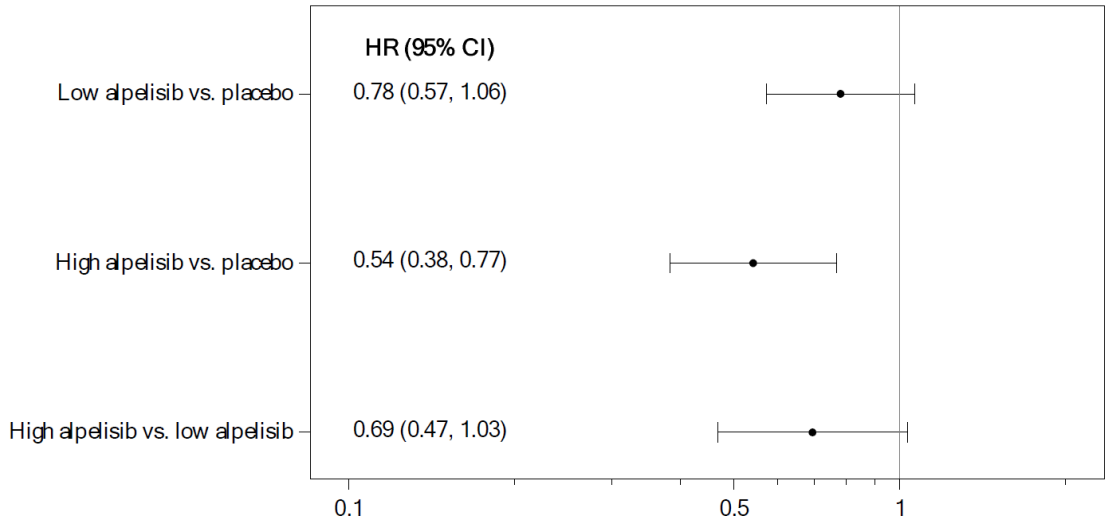
Source: Appendix 1-Figure 3-27

Figure 19: Kaplan-Meier plot of PFS by median dose intensity in the PIK3CA mutant cohort – Study C2301 (FAS)



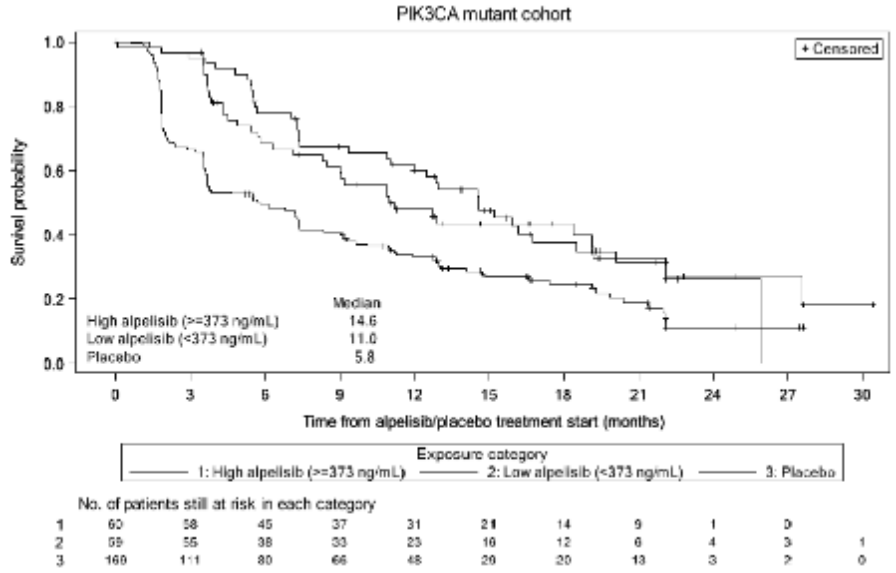
Source: Appendix 1-Figure 3-29

Figure 20: Kaplan-Meier plot of PFS by median dose intensity (first 4 weeks) in the PIK3CA mutant cohort – Study C2301 (FAS)



Source: Appendix 1-Figure 3-28

Figure 21: Forest plot of hazard ratios with 95% CI for PFS by median time-normalized projected Ctrough in the PIK3CA mutant cohort in study C2301 (FAS)



Source: Appendix 1-Figure 3-23

Figure 22: Kaplan-Meier plot of PFS by median time-normalized projected Ctrough in the PIK3CA mutant cohort – Study C2301 (FAS)

Exposure-safety analysis

- Hyperglycaemia

Overall, the analyses consistently indicated increasing exposure was associated with increasing risk of hyperglycemia (grade 2 or worse). Hence, dose reductions are appropriate to reduce the risk of hyperglycemia. The Phase I analysis also showed a relationship between the risk of hyperglycemia and

baseline fasting plasma glucose, indicating that subjects with greater baseline value are at a greater risk of developing hyperglycemia when receiving alpelisib.

Phase I pool

Results showed that increasing exposure (AUC0-24) by 50% the risk of hyperglycemic event (grade 2 or worse) increases by 74.7% (HR=1.747, 95% CI: 1.333, 2.290). Increasing baseline FPG by 1 mmol/L unit similarly increases the risk by 75.8% (HR=1.758, 95% CI: 1.449, 2.113) (Appendix 1-Table 3-33).

Phase III

The results showed that increasing exposure by 50% (TN-Ctrough) increased the risk of hyperglycemic events by 22.3% (HR=1.223, 95% CI: 1.014, 1.475) for grade 2 or worse and by 33.1% (HR=1.331, 95% CI: 1.058, 1.675) (grade 3 or worse). Using the instantaneous Ctrough showed an attenuation of the risk.

- Rash

Overall, the analyses showed a trend between an increase in plasma exposure and the risk of rash though differences were observed between the Phase I study pool and the Phase III data. This was mainly due to a wider range of doses studied in Phase I.

Phase I pool

Results showed that by increasing exposure (AUC0-24) by 50% the risk of a rash event (grade 2 or worse) increases by 40.6% (HR=1.406, 95% CI: 1.083, 1.826). No difference was detected between monotherapy and combination with fulvestrant with respect to the probability of rash.

Phase III

The impact of alpelisib exposure, characterized by either TN-Ctrough (time-dependent covariate) or instantaneous Ctrough (fixed covariate) on rash (at least grade 2 and at least grade 3) was investigated using a Cox regression model in Study C2301. A trend towards higher risk of rash was shown with increasing TN-Ctrough; 50% in TN-Ctrough increases the risk of a least Grade 2 rash by 16% (HR=1.160, 95% CI: 0.907, 1.485), and 15% for at least Grade 3 rash (HR=1.150, 95% CI: 0.841, 1.574). The instantaneous effect of Ctrough showed a small increase in the risk of rash by 4-8% for an increase in instantaneous Ctrough by 50%.

The different use of exposure metrics was justified due to differences in the sampling schedule between Phase I and Phase III studies. Overall, equal exposure-safety relationships were established and differences in the mathematical relationships were associated to differences in population, PK metrics and associated variability.

2.4.4. Discussion on clinical pharmacology

Piqray is for oral use. The tablets should be swallowed whole and should not be chewed, crushed or split. Tablets that are broken, cracked or otherwise not intact should not be ingested.

The pharmacokinetics properties of alpelisib were investigated in patients under an oral dosing regimen ranging from 30 to 450 mg daily. Healthy subjects received single oral doses ranging from 300 to 400 mg.

The methodology applied to characterise the pharmacokinetics and interactions through non-compartmental analysis and population approach is generally acceptable.

In general, the pre-study validations of the analytical methods are satisfactory and demonstrated adequate precision y accuracy (both intra- and inter-run) within the calibration range. The bioanalytical methods also showed and adequate sensitivity, selectivity, matrix effect and no-carry-over effect. In addition, the analyte stability was demonstrated.

No bioavailability study in humans was provided. The oral absorption and bioavailability of alpelisib was characterised using data from other clinical and non-clinical studies and supported by an absorption model. This alternative approach is considered acceptable.

In the ADME study 400 mg alpelisib was administered in four fasting healthy subjects. The Tmax in this study was similar to the results obtained in studies conducted in non-fasting patients. However, the Cmax and AUC0-24 were lower than in non-fasting subjects. Based on the food effect study, it is recommended that the drug is taken with food where the absorption is almost doubled and the variation lower. The lower absorption in the mass balance study is not suspected to impact the results on distribution, metabolism and excretion. However, a study under fed conditions would have been preferred as expected to be more sensitive.

The population pharmacokinetics of alpelisib have been described using a one-compartment model with first-order absorption, distribution and elimination, including several covariates affecting CL/F and V/F. The adequacy of the model is considered acceptable based on the model performance and final parameter estimates. The clinical relevance of different covariates was assessed.

Overall, the pharmacokinetics were comparable in both oncology patients and healthy subjects.

Based on the provided data, it is considered that there is dose proportionality for AUC and Cmax across doses, which also includes the proposed treatment dose of 300 mg. However, it is noted that the inter-subject variability for AUC0-24 and AUClast increase with increasing doses which is also true for Cmax. After repeated daily administration, alpelisib accumulates in plasma (between 1.3- and 1.5-fold) with steady state reached by day 3. The accumulation ratio is not considered clinically relevant. There is no evidence of time dependency.

No studies have been conducted to investigate the impact of genetic polymorphism on PK. As the metabolism of alpelisib is mainly by non-CYP dependent hydrolysis, it is not expected that genetic polymorphism will affect the metabolism of alpelisib.

Based on the provided data, alpelisib absorption is affected by food. Safety, efficacy and PK (including dose proportionality) of alpelisib have been established in the fed state in patients with cancer in submitted studies. Data indicates that the exposure to alpelisib is increased by any meal. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is the potential cause of the food effect. Hence, Piqray should be taken immediately after food at approximately same time each day. (see SmPC sections 4.2 and 5.2).

If a dose of Piqray is missed, it can be taken immediately following food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, Piqray should be taken at the usual time. If the patient vomits after taking the Piqray dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a low-fat low-calorie (LFLC) meal, AUC_{inf} was decreased on average by 21% and C_{max} by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUC_{inf} and a 51% decrease in C_{max} with ranitidine compared to the fasted state without co-administration of ranitidine. Population pharmacokinetic analysis showed no significant

effect of co-administration of acid-reducing agents, including proton pump inhibitors, H2 receptor antagonists and antacids, on the pharmacokinetics of alpelisib. It is agreed that the clinical impact of ranitidine on alpelisib PK might be of minor relevance (around 20% change in AUC and Cmax) as long as alpelisib is taken immediately after food. Therefore, alpelisib can be co-administered with acid-reducing agents, provided alpelisib is taken immediately after food (see SmPC sections 4.2 and 4.5).

With regards to special population, the population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight, or gender on the systemic exposure of alpelisib that would require dose adjustment (see SmPC section 5.2).

Pharmacokinetic data was derived only from adult. This is reflected in section 5.2 of the SmPC.

Of 284 patients who received Piqray in the phase III study (in the alpelisib plus fulvestrant arm), 117 patients were ≥65 years of age and 34 patients were between 75 and 87 years of age. Overall, there are limited data in patients aged ≥75 years, and especially in those ≥85 years.

Based on PK modelling, no dose regimen adjustment is required in patients aged 65 years or above. (see SmPC sections 4.2 and 5.2).

Population pharmacokinetic analyses and pharmacokinetic analyses from a phase I study in Japanese cancer patients showed that there are no clinically relevant effects of ethnicity on the systemic exposure of Piqray. Non-compartmental pharmacokinetic parameters after single and multiple daily doses of Piqray for Japanese patients were very similar to those reported in the Caucasian population (see SmPC section 5.2).

Based on the results from Study A2105, a pharmacokinetic study conducted with hepatic impairment, moderate and severe hepatic impairment had negligible effect on the exposure of alpelisib. The mean exposure for alpelisib was increased 1.26 fold in patients with severe (GMR: 1.00 for Cmax; 1.26 for AUClast/AUCinf) hepatic impairment. Differences in AUC and Cmax of alpelisib were not statistically different across the different sub-groups of population in this study. Similar results were observed on the population PK analysis that included 230 patients with normal hepatic function, 41 patients with mild hepatic impairment and no patients with moderate hepatic impairment, further supporting the findings from the dedicated hepatic impairment study, mild and moderate hepatic impairment had no effect on the exposure of alpelisib. Overall, no dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child Pugh class A, B or C, respectively) based on a hepatic impairment study in non-cancer subjects with impaired hepatic function (see SmPC sections 4.2 and 5.2).

Based on the population pharmacokinetic analysis that included 117 patients with normal renal function (eGFR ≥90 ml/min/1.73 m^2) / (CLcr ≥90 ml/min), 108 patients with mild renal impairment (eGFR 60 to <90 ml/min/1.73 m^2)/ (CLcr 60 to <90 ml/min), and 45 patients with moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of alpelisib (see SmPC section 5.2). The observed differences in AUC and Cmax due to renal impairment were justified by differences in age. Exposure differences across the age sub-groups of population were less than 20%, which can be considered no clinically relevant. Overall, it is concluded that no dose adjustment is necessary in patients with mild or moderate renal impairment (see SmPC sections 4.2 and 5.2). Caution should be used in patients with severe renal impairment as there is no experience with Piqray in this population.

The interaction effects of alpelisib on different enzymatic substrates was deeply evaluated using *in vitro*, *in silico* and *in vivo* data. The effect of different enzymatic inhibitors or inducers and the co-administration of fulvestrant was also assessed. The results suggest minor impact at the expected

exposure range of alpelisib administration on the other substrates and minor changes of alpelisib concentrations when co-administered with other drugs.

CYP3A4 is the predominant enzyme involved in the metabolism of alpelisib, however the overall contribution of CYP3A metabolism was considered low with an estimated fm of 12%. *In vitro* studies indicated that alpelisib may induce CYP2B6, CYP2C9 and CYP3A, may inhibit CYP2C8, CYP2C9, CYP2C19, and that alpelisib is a time-dependent inhibitor of CYP3A4 (see non-clinical data). The Applicant provided a sensitivity analysis where the fraction metabolized (fm) via CYP3A4 ranged from 0.12 to 0.207. Predicted changes in AUC ratios with ritonavir and rifampicin were 27% higher and 25% lower compared to fm=0.12. Based on the results from the worst-case scenario, the impact of co-administrated strong CYP3A4 inhibitors or inducers is considered of low clinical concern. In conclusion, although the effects of CYP3A4 inducers or inhibitors have not been evaluated in clinical studies, no clinically meaningful changes in overall exposure are expected as a result of the low fraction (<15%) metabolised by CYP3A4.

Simulation of the induction potential of alpelisib of CYP2C9 indicated a maximum effect of 0.2 change of warfarin AUC after concomitant alpelisib 300 mg qd. However, this result is not supported by clinical data and the PBPK modelling platform was not fully validated to predict alpelisib induction potential on CYP2C9. Therefore, caution is recommended when alpelisib is used in combination with CYP2C9 substrates with narrow therapeutic index (see SmPC section 4.5).

Additionally, no clinical data of CYP2B6 interaction are available from clinical studies. Static mechanistic risk assessments were carried out with sensitive CYP2B6 substrates to evaluate alpelisib potential for CYP2B6 induction. As a result of the assessments, a reduction of bupropion exposure by up to 3-fold can be expected when co-administered with alpelisib. Therefore, sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with Piqray.

In vitro interaction studies showed that pharmacokinetic interactions by P-gp, BCRP and OAT3 are expected in patients. The risk of interactions of alpelisib with P-gp, BCRP and OAT3 transporters are adequately described in sections 4.5 and 5.2 of the SmPC (see also discussion on non-clinical aspects).

The major metabolite BZG791 inhibited CYP2C8 and induced CYP2C9 and CYP2B6. BZG791 was a medium strong inhibitor of OATP1B1 (Ki 8.59 µM) and a strong inhibitor of OAT3 (Ki 1.38 µM). However, no clinically relevant exposure changes are expected from these interactions.

Since alpelisib is an inducer and an inhibitor of CYP3A4, the effect of alpelisib on CYP3A4 enzymes was investigated in both a clinical DDI study and PBPK simulations and it was concluded that no clinically meaningful change is expected as a result of drug interaction with CYP3A4 substrates. Therefore, no dose adjustment is required when co-administering Piqray with CYP3A4 substrates. The results from the drug-drug interaction study in which alpelisib was co administered with everolimus, a sensitive CYP3A4 substrate, confirmed that there are no clinically significant pharmacokinetic interactions (increase in AUC by 11.2%) between alpelisib and CYP3A4 substrates. No change in everolimus exposure was observed at alpelisib doses ranging from 250 to 300 mg. No dose adjustment is required when co administering Piqray with CYP3A4 substrates (e.g. everolimus, midazolam).

Caution is recommended when Piqray is used in combination with CYP3A4 substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib) (see SmPC section 4.5).

Overall, potential pharmacokinetic interactions mediated by the interaction of alpelisib and its main metabolite M4 with CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 are adequately described in the SmPC. Inhibition of CYP2C8 by alpelisib at clinically relevant concentrations can be discarded based on

the result of a clinical trial (Study CBYL719Z2101, data not shown) that showed that the PK of paclitaxel (a CYP2C8 substrate) was unaffected by alpelisib (Rodon et al 2018).

No clinical studies were conducted assessing the drug-drug interaction potential between alpelisib and hormonal contraceptives.

Results from study X2101, in which monotherapy and concomitant treatment with fulvestrant was tested, were presented. There did not seem to be a larger benefit of the maximal tolerated dose (400 mg) compared with 300 mg dose. The Applicant argued that overall response rates for alpelisib in monotherapy occurred at alpelisib doses of 270 mg or above. Furthermore, it was argued that constant inhibition of the PI3K pathway can only be obtained at single-agent dose levels of 300 mg or above. Therefore, the starting dose of 300 mg was chosen. The justification by the Applicant of the selected dose of 300 mg is considered acceptable.

The Applicant has sufficiently justified the pharmacodynamic interaction between alpelisib and fulvestrant. The Applicant discussed that the activated PI3K pathway has a prominent role in the development of endocrine resistance and estrogen-independent tumor growth. Targeting the activated PI3K pathway in ER positive tumours may therefore reverse the loss of ER expression and signalling and restore the hormonal sensitivity. Concomitant targeting of the PI3K/AKT/mTOR and the ER pathway was therefore proposed.

The exposure response analysis did not show any statistical significant association between exposure and progression free survival, which might be due to short half-life and thereby small differences in Ctrough making the analysis unable to show statistical significant results.

An exposure-safety analysis was conducted in order to assess the development of hyperglycaemia and rash in patients. The exposure-QTc analysis did not show any QTc prolongation along the expected alpelisib exposure range.

2.4.5. Conclusions on clinical pharmacology

The assessment of the clinical pharmacology properties of alpelisib is acceptable. The adequacy of the analytical methods, pharmacokinetic properties, population pharmacokinetic model and interaction effects have been demonstrated.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dose selection was mainly based on a single first in-human phase I clinical trial, with some additional input from a similar trial performed in Japanese patients, three investigator-initiated trials and another Novartis-sponsored study.

Selection of the alpelisib 300 mg daily continuous dosing schedule was based on the results of the first in-human Study X2101, where alpelisib was administered both as a single agent and in combination with fulvestrant in the BC subset.

134 adult subjects with advanced solid malignancies whose tumors had an alteration (mutation or amplification) of the PIK3CA gene were treated with increasing doses of oral alpelisib (30 mg to 450 mg once daily or 120 mg to 200 mg twice daily). The maximum tolerated dose (MTD) was determined to be 400 mg.

87 subjects with heavily pretreated ER-positive, HER2-negative metastatic breast cancer were treated with alpelisib (300 mg, 350 mg, and 400 mg once daily) in combination with fulvestrant at the approved dose and schedule of 500 mg on Days 1 and 15 of the first cycle and Day 1 of subsequent cycles. The MTD for alpelisib in combination with fulvestrant was found to be the same as in monotherapy, that is 400 mg daily.

Nevertheless, the recommended dose for further development was determined to be 300 mg based on the following information:

1. Similar levels of pharmacodynamic and clinical activity were observed among 300 mg, 350, mg and 400 mg of alpelisib plus fulvestrant.
2. Exposure-safety analysis results confirmed a positive association between exposure and the risk of developing grade ≥ 2 hyperglycaemia or rash.
3. Median relative dose intensity was in fact lower for the subjects receiving 400 mg (89.3%) than among those assigned to the lower 300 mg stratum (99.5%), due to lower rates of dose adjustment and/or interruption (33.3% vs 71.4%) or drug discontinuation (0% vs 12.9%)

Thus, the clinical and proposed commercial dosage of alpelisib film-coated tablets in combination with fulvestrant is 300 mg once daily with dose reduction allowed to manage adverse events (AEs) in 50 mg increments to 250 mg or 200 mg once daily. The three proposed commercial strengths of alpelisib FCT are 50 mg, 150 mg, and 200 mg.

2.5.2. Main study

Study CBYL719C2301 (SOLAR-1)

Study C2301 is a randomized, double-blind, placebo-controlled, international, multicenter Phase III study to determine whether treatment with alpelisib plus fulvestrant prolongs PFS relative to placebo plus fulvestrant in patients with advanced breast cancer harboring a PIK3CA mutation following progression of disease while on or after an endocrine-based treatment.

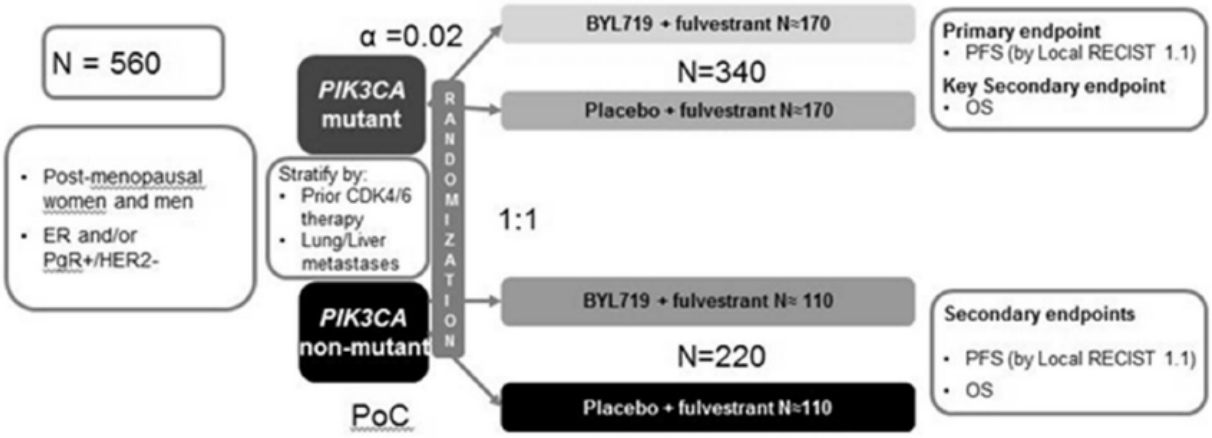


Figure 23: Study design - Study CBYL719C2301

This study consisted of four phases: screening phase (35 days), randomized treatment phase, post-treatment follow-up (for safety and efficacy follow-ups), and post-treatment survival follow-up.

Methods

Study Participants

Patients were recruited in 275 sites across 33 countries as follows: Argentina (6), Australia (5), Austria (4), Belgium (7), Brazil (8), Bulgaria (5), Canada (9), Chile (4), Czech Republic (5), Denmark (6), France (17), Germany (24), Greece (4), Hong Kong (1), Hungary (5), India (4), Israel (5), Italy (16), Japan (14), Republic of Korea (7), Lebanon (3), Mexico (3), Netherlands (3), Peru (3), Portugal (4), Romania (6), Russian Federation (5), Spain (20), Sweden (5), Taiwan, Province of China (3), Thailand (2), United Arab Emirates (1), United Kingdom (6) and United States (55).

Inclusion criteria

- Adults ≥ 18 years old who provided written informed consent to participate in the study
- Able to provide adequate tumour tissue (either archival tissue or new tumour biopsy, preferably after the most recent progression or recurrence) for the analysis of PIK3CA mutational status.
- Female patients must be postmenopausal defined either by: prior bilateral oophorectomy; age ≥ 60; age < 60 and amenorrhoeic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression, and follicle-stimulating hormone (FSH) and oestradiol levels in the postmenopausal range per local normal range.
- Radiological or objective evidence of recurrence or progression during or after AI therapy.
- Histologically and/or cytologically confirmed diagnosis of ER-positive and/or Progesterone receptor-positive breast cancer.
- Patient either had measurable disease, i.e. at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or, if no measurable disease was present, then at least one predominantly lytic bone lesion must be present.
- Patient had advanced (locoregionally recurrent not amenable to curative therapy or metastatic) breast cancer.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

- Adequate bone marrow and organ function as defined by: absolute neutrophil count ≥ 1.5 × 10^9 /L; Platelets ≥ 100 × 10^9 /L; Haemoglobin ≥ 9.0 g/dL; Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 according to the National Cancer Institute (NCI)'s - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 if judged clinically not significant by the Investigator; Potassium within normal limits, or corrected with supplements; International normalized ratio (INR) ≤ 1.5; Creatinine clearance ≥ 35 mL/min using Cockcroft-Gault formula; In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5-times the upper limit of the normal range (× ULN). If the subject had liver metastases, ALT and AST ≤ 5 × ULN; Total bilirubin < ULN except for subjects with Gilbert's syndrome who may only be included if the total bilirubin was ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN; Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L)* and glycosylated haemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met); Fasting serum amylase ≤ 2 × ULN; Fasting serum lipase ≤ ULN [*Recommendation added in protocol amendment #2: For subjects with FPG ≥ 100 mg/dL and/or HbA1c ≥ 5.7% (i.e. threshold for pre-diabetes) at screening, lifestyle changes are recommended according to the American Diabetes Association (ADA) guidelines. In the original protocol, the HbA1c criterion was <8%. The HbA1c criterion was changed to <6.5% in protocol amendment #1, and to <6.4% in protocol amendment #2].

Exclusion criteria

Patients eligible for this study must have not met any of the following criteria:

- With inflammatory breast cancer at screening.
- With symptomatic visceral disease or any disease burden making the patient ineligible for endocrine therapy.
- Received prior treatment with chemotherapy or concurrently using other anticancer therapy.
- Known hypersensitivity to alpelisib or fulvestrant or to any of the excipients.
- Had surgery within 14 days prior to starting study drug or had not recovered from major side effects.
- Had not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 grade ≤ 1.
- With Child-Pugh score B or C.
- Had received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who had not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or from whom ≥ 25% of the bone marrow was irradiated.
- Had concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
- Patient had central nervous system (CNS) involvement. If patient fulfilled the following 3 criteria she/he was eligible for the trial: Completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study and, CNS tumour was clinically stable at the time of screening and patient did not receive steroids and/or enzyme inducing anti-epileptic medications for brain metastases.

- With an established diagnosis of diabetes mellitus type I or uncontrolled type II (based on FPG and HbA1c, see inclusion criterion)
- Had impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of the study drugs
- Had a known history of Human Immunodeficiency Virus (HIV) infection
- Had any other concurrent severe and/or uncontrolled medical condition that could contraindicate subject participation in the clinical study
- Had currently documented pneumonitis
- Had clinically significant, uncontrolled heart disease and/or recent cardiac events including any history of heart disease.
- Receiving or had received systemic corticosteroids ≤ 2 weeks prior to starting study drug.
- Sexually active males unless they were sterilized (at least 6 months prior to screening) or use a condom during intercourse while taking drug and for at least 8 months after stopping alpelisib and/or fulvestrant medication and should not father a child in this period.
- Participation in a prior investigational study within 30 days prior to the start of study treatment or within 5 half-lives of the investigational product, whichever was longer.
- History of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
- Patients who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease.

Determination of PIK3CA mutation status

During the screening phase, tumour samples were collected by the investigational sites and shipped to the designated central laboratory to establish the PIK3CA mutation status prior to randomization. The PIK3CA mutation status was identified by analysing the PIK3CA gene for hotspots known to impact PI3K function in exons 7, 9, and 20, anticipated to cover the majority of the PIK3CA mutations identified in patients with HR-positive breast cancer. PIK3CA non-mutant status was defined as follows: all analyses for PIK3CA mutation were interpretable and showed no evidence of a mutation in the PIK3CA gene for the defined hotspots in exons 7, 9, and 20. If the analysis for the PIK3CA gene mutation was not fully interpretable, i.e. at least one hotspot provided a non-interpretable result, the subject was not eligible for the study.

PIK3CA mutation testing was to be performed on formalin-fixed, paraffin-embedded (FFPE) tumour biopsy specimens, from either initial diagnosis or the most recent biopsy, utilising the Novartis PIK3CA PCR mutation CTA. When enrolment for the PIK3CA non-mutant cohort was substantially complete, C2301 mutation screening transitioned to the QIAGEN therascreen PIK3CA RGQ PCR Kit, the companion diagnostic (CDx) developed for alpelisib (hereafter referred to as Tissue CDx).

Treatments

Study treatment was double-blinded. Patients were randomized in a 1:1 ratio within each cohort (PIK3CA mutant and PIK3CA non-mutant) to receive either:

A. Alpelisib plus fulvestrant arm

Alpelisib 300 mg orally q.d continuously + Fulvestrant 500 mg i.m. on Days 1 and 15 of Cycle 1 and on Day 1 ± 3 days of a 28-day cycle thereafter

B. Placebo plus fulvestrant arm

Alpelisib-matching placebo 300 mg orally q.d continuously + Fulvestrant (same schedule as study arm A)

Patients were treated until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

Treatment crossover from placebo plus fulvestrant to alpelisib plus fulvestrant was not permitted in this study.

For patients who did not tolerate the protocol-specified dosing schedule, dose adjustments were permitted for alpelisib/placebo. No dose modification for fulvestrant was permitted.

A maximum of two dose reductions (to 250 mg and to 200 mg) was allowed, after which the patient was to be discontinued from treatment with alpelisib/placebo. Dose reduction was based on the worst preceding toxicity.

Table 25: Dose reduction sequential steps for alpelisib/placebo

Alpelisib/placebo dose level	Dose and schedule	Number of tablets & strength
Starting dose	300 mg/day continuously	1 x 200 mg tablet and 2 x 50 mg tablet
Dose level -1	250 mg/day continuously	1 x 200 mg tablet and 1 x 50 mg tablet
Dose level -2	200 mg/day continuously	1 x 200 mg tablet

After treatment with alpelisib/placebo was resumed at a lower dose due to toxicity:

- If the same toxicity reoccurred with the same severity, then the dose was to be lowered one more level during the next treatment re-initiation irrespective of the duration it took for resolution.
- Once the alpelisib/placebo dose had been reduced, no re-escalation was allowed, even upon resolution of the AE.

If a patient required a dose delay of alpelisib/placebo for > 28 days then alpelisib/placebo was permanently discontinued, but treatment with fulvestrant could continue. All scheduled assessments also continued. If fulvestrant was withheld for > 35 days since a planned injection, then fulvestrant was permanently discontinued. Patients could continue treatment with alpelisib/placebo at the discretion of the Investigator until study completion and all scheduled assessments were performed.

Medications required to treat AEs, manage cancer symptoms, concurrent diseases, and supportive care agents, such as pain medications, anti-emetics, and antidiarrheals were allowed.

The use of bisphosphonates/denosumab, regardless of indication, was allowed if patients had been taking stable doses for at least 2 weeks prior to randomization and continued on a stable dose during the treatment period. Patients requiring new initiation of bisphosphonates/denosumab during the course of the study could continue study treatment if disease progression could be completely ruled out and was clearly documented in the subjects' source documentation.

The following medications were prohibited during combined alpelisib/placebo and fulvestrant treatment in this study:

- Medications with a known risk for TdP
- Other investigational and antineoplastic therapies

- Herbal preparations/medications and dietary supplements (except for vitamins).

Co-administering QT prolonging drugs or drugs with potential QT prolongation was to be avoided where possible. If concomitant administration of drugs with a known potential to cause TdP was required, study treatment was interrupted until an assessment of the potential safety risk had been performed.

Objectives

Primary objective

- To determine whether treatment with alpelisib in combination with fulvestrant prolongs progression-free survival (PFS) based on local investigator assessment compared to treatment with placebo in combination with fulvestrant for patients with PIK3CA mutant advanced breast cancer.

Secondary objectives

Key secondary objective

- To determine whether treatment with alpelisib in combination with fulvestrant prolongs overall survival (OS) compared to treatment with placebo in combination with fulvestrant for subjects with PIK3CA mutant advanced breast cancer.

Other secondary objectives

- To establish proof of concept of treatment benefit with alpelisib in combination with fulvestrant with respect to PFS for subjects with PIK3CA non-mutant status.
- To evaluate the two treatment arms with respect to OS for subjects with PIK3CA nonmutant status.
- To evaluate the two treatment arms and cohorts of interest with respect to overall response rate, clinical benefit rate.
- To evaluate the two treatment arms and cohorts of interest with respect to time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status.
- To evaluate the safety and tolerability of alpelisib in combination with fulvestrant.
- To evaluate the change in global health status/QOL in the two treatment arms and cohorts of interest.
- To characterize the pharmacokinetics (PK) of fulvestrant and alpelisib when given in combination with fulvestrant.
- To evaluate the association between PIK3CA mutation status as measured in circulating tumour deoxyribonucleic acid (ctDNA) at baseline with PFS upon treatment with alpelisib.

Exploratory objectives included: to describe time to response and duration of response in the two treatment arms and cohorts of interest; to explore exposure/response relationships; to explore potential differences in hospital resource utilization in the two treatment arms and cohorts of interest; to explore changes in patient-reported global health status and pain in the two treatment arms and cohorts of interest; to assess molecular alterations/characteristics associated with response, resistance to treatment and/or safety; to explore the potential role of ctDNA as surrogate endpoint for monitoring disease response; to explore the benefit of alpelisib in bone lesions; to explore the long-term benefit

intermediate to PFS and OS (the endpoint to evaluate the long-term benefit intermediate to PFS and OS is progression on next-line therapy (PFS2)).

Outcomes/endpoints

Primary endpoint: PFS in the PIK3CA mutant cohort for the FAS based on local radiology assessment. PFS was defined as the time from the date of randomization to the date of first documented progression or death due to any cause.

PFS was censored at the last adequate tumour assessment if a patient did not have an event or the event occurred after two or more missing tumour assessments. In the primary analysis, PFS was not censored if a new antineoplastic therapy was started; instead, an intent-to-treat (ITT) approach was used and this new antineoplastic therapy was ignored for the purposes of PFS derivation (and tumour assessments continued).

Sensitivity analyses were performed if the analysis of the primary endpoint in the PIK3CA mutant cohort showed statistically significant results, including repeating the primary PFS analysis using the PPS, using different censoring rules, and using an unstratified log-rank test to compare the two treatment arms.

A stratified, multivariate Cox regression model was fitted to evaluate the effect of other baseline demographic or disease characteristics on the estimated hazard ratio.

Tumour response was assessed locally and centrally (BIRC) based on RECIST 1.1. The primary efficacy assessment used to determine PFS was based on the local (i.e. Investigator) radiology review of tumour assessments and was used for treatment decision making. To support the primary endpoint, a central review of the scans was carried out only for the PIK3CA mutant cohort. Following an audit-based approach, all scans from approximately 50% of randomly selected randomized subjects underwent review. If consistency in the treatment effect was not established between the investigator assessment and the selected audit sample, a full read of imaging data could follow.

Key secondary endpoint: Overall Survival (OS) in patients of the PIK3CA mutant cohort. OS was defined as the time from date of randomization to date of death due to any cause.

Other secondary endpoints: PFS and OS in the PIK3CA non-mutant cohort; PFS by PIK3CA mutant status as measured in ctDNA; Overall response rate defined as the proportion of subjects with best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1; Clinical benefit rate defined as the proportion of subjects with a best overall response of CR or PR or SD or Non-CR/Non-PD lasting 24 weeks or more based on local Investigator assessment according to RECIST 1.1 criteria; Clinical response by PIK3CA mutant status as measured in ctDNA Time to definitive deterioration defined as an increase in ECOG PS by at least one category from the Baseline score or death due to any cause; change from baseline and time to 10% deterioration in global health status/QoL score of the EORTC QLQ-C30.

Exploratory endpoints: Patient-reported outcomes (PROs) for HRQoL analysed over time based on theEQ-5D-5L, and BPI-SF.

Sample size

Median PFS in the fulvestrant arm (control arm) was assumed to be 6.5 months (Di Leo et al 2010). For the overall population in the PIK3CA mutant cohort, the median PFS in the control arm (fulvestrant plus placebo) was estimated via simulation to be around 7.0 months. For the overall population in the PIK3CA non-mutant cohort, the median PFS in the control arm (fulvestrant plus placebo) was estimated via simulation to be around 7.4 months.

It was expected that treatment with alpelisib plus fulvestrant in both cohorts would result in a 40% reduction in the hazard rate (corresponding to an increase in median PFS from 7.0 months to 11.67 months in the PIK3CA mutant cohort and from 7.4 months to 12.33 months in the PIK3CA non-mutant cohort, under the exponential model assumption).

In the PIK3CA mutant cohort, a total of 243 PFS events were required to have 83.8% power at a one-sided overall 2.0% level of significance to reject the null hypothesis. Assuming that 40% of the subjects would have a PIK3CA mutant status, and a 10% follow-up loss rate, a total of 340 subjects would need to be randomized in this cohort to the two treatment arms in a 1:1 ratio.

In patients with PIK3CA non-mutant status, the proof of concept criteria required a minimum of 102 PFS events and a final figure of 220 subjects was required for randomisation.

Randomisation

After confirmation of the eligibility criteria, patients were assigned to one of the two cohorts (PIK3CA mutant or PIK3CA non-mutant based on tissue testing). Patients in each cohort were randomized to one of the two treatment arms using a 1:1 ratio and were stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s).

In addition, the IRT will manage the limitation of the number of patients with prior CDK4/6 inhibitors treatment up to 30% of the total number of the patients. If the study was to continue in both cohorts to the final analyses, the maximum total number of CDK4/6 inhibitors pre-treated patients was to be 168.

Blinding (masking)

This was a double-blind study. Until the database for the final PFS analysis in the PIK3CA mutant cohort was locked, treatment arm assignment was kept blind to study subjects, Novartis Study team, investigators, local radiologists and central radiology reviewers.

An independent Data Monitoring Committee reviewed semi-blinded safety and efficacy data. Efficacy and safety outputs were provided to the independent Data Monitoring Committee (DMC) with the two treatment arms identified as 'Treatment 01' and 'Treatment 02.' However, the identity of each treatment arm was not shared with the DMC. The DMC chair had the option to open the envelope containing the identity of each treatment arm during the course of DMC review if needed.

The PIK3CA mutation status was also blinded to the investigators and the subjects.

Statistical methods

Analysis sets

All efficacy analyses were performed using Full Analysis Set (FAS) which consisted of all randomized patients. According to the intent to treat principle, patient data were analysed according to the treatment and stratum they had been assigned to at randomization. The FAS was the main population for analyses of subject disposition, demographics, and other baseline characteristics. The FAS was also the primary population for the efficacy analyses.

The Per-protocol set (PPS) comprised of all patients in the FAS for the PIK3CA mutant cohort who did not have any protocol deviations that confounded the interpretation of the primary analyses conducted on the FAS. The PPS was used to perform a sensitivity analysis for the primary efficacy endpoint (i.e. PFS in the PIK3CA mutant cohort) if the primary endpoint was statistically significant.

Statistical hypothesis, model, and method of analysis

The primary efficacy analysis was the comparison of the distribution of PFS between the two treatment groups using a stratified log-rank test at a one-sided 2.0% level of significance in the PIK3CA mutant cohort. A group sequential design with Haybittle-Peto boundaries was used to control the overall type-I error rate. A maximum of three analyses was planned; one futility interim analysis after observing approximately 97 PFS events (corresponding to a 40% information fraction), one interim analysis for superiority after observing approximately 185 PFS events (76% information fraction), and a final PFS analysis after observing approximately 243 events.

The PFS survival distribution was estimated using Kaplan-Meier methodology. The PFS hazard ratio with two-sided 95% confidence interval (CI) was derived from the stratified Cox proportional hazards model.

The key secondary efficacy endpoint was the comparison of the distribution of OS between the two treatment groups in the PIK3CA mutant cohort. A hierarchical testing strategy was used to control the overall type-I error rate, where OS was to be statistically evaluated and interpreted only if the primary efficacy endpoint PFS was significantly different between the two treatment groups.

Up-to 3 analyses of OS were planned. A Lan-DeMets (O'Brien-Fleming) (Lan and DeMets 1983) alpha-spending function was used to control for type-I error rate inflation.

PFS in the PIK3CA non-mutant cohort was analysed as a secondary endpoint and the treatment effect in this cohort was considered to be clinically relevant if: the estimated HR (stratified according to presence of lung/liver metastases and previous treatment with CDK4/6 inhibitors) ≤ 0.60 and the posterior probability (HR < 1) ≥ 90%. If both criteria were met then the comparison of PFS between the two treatment arms in this cohort using a stratified log-rank test at a one-sided 0.5% level of significance, was to be made. OS analyses were to be performed only if PFS in this cohort met the PoC criteria and was statistically significant. An analysis of PFS based on local radiology assessments and using RECIST 1.1 criteria with PIK3CA mutant status as measured in ctDNA at baseline, was conducted using the same analytical conventions as the primary PFS analysis.

ORR was calculated based on the FAS using Investigators' review of tumour assessment data for each cohort. Subjects with only non-measurable disease at baseline were part of the analysis and were included in the numerator only if a CR was observed.

Results

Participant flow

Since 23-Jul-2015, 572 patients have been enrolled in 275 sites across 33 countries, 341 in the PIK3CA mutant cohort and 231 in the PIK3CA non-mutant cohort. As of that date, the majority of patients in the alpelisib plus fulvestrant arm (75.1%) and in the placebo plus fulvestrant arm (80.8%) had discontinued study treatment, mostly due to progressive disease (55.0% in the alpelisib plus fulvestrant arm vs. 68.0% in the placebo plus fulvestrant arm).

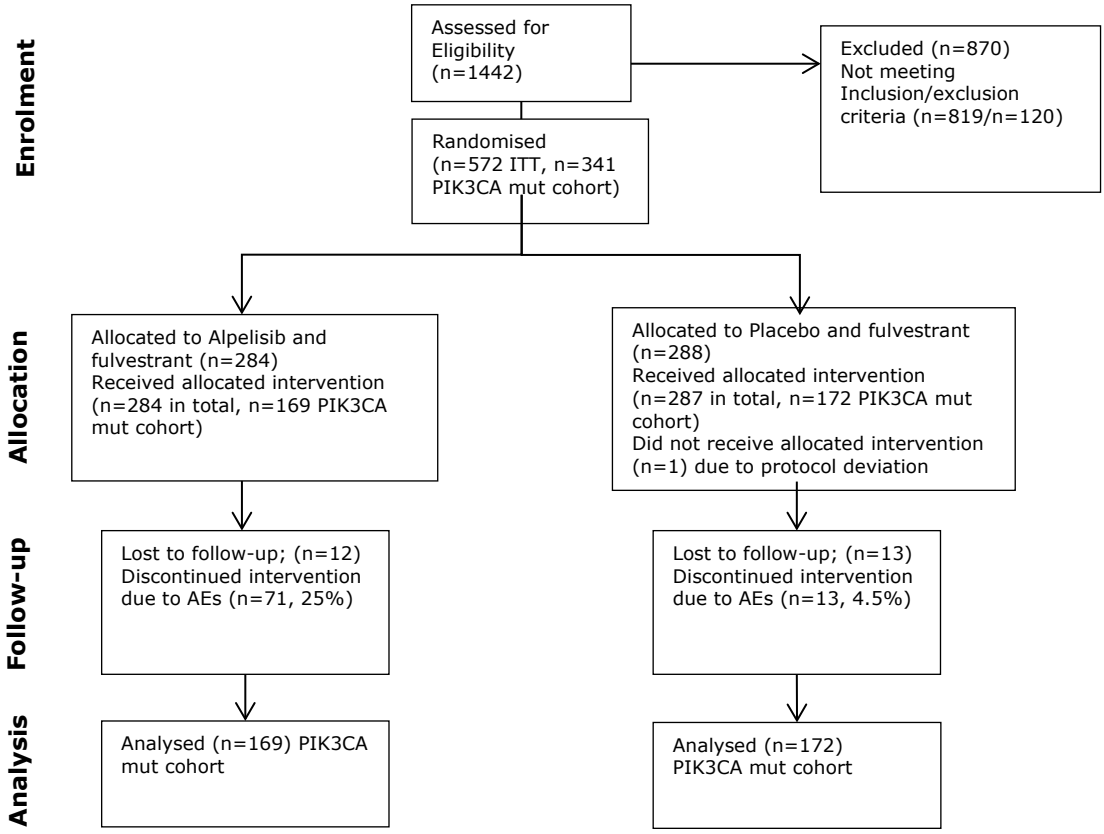


Figure 24: Participant flow - Study C2301

Table 26: Screening phase disposition (all screened patients) - Study C2301

Disposition/reason	All subjects N=1442 n (%)
Completed screening phase	572 (39.7)
Discontinued prior to screening phase completion	870 (60.3)
Primary reason for not completing screening phase	
Screen failure	808 (56.0)
Subject/guardian decision	55 (3.8)
Physician decision	6 (0.4)
Adverse event	1 (0.1)

Percentage is out of total number screened

The number of screen failures were high (n=808), and were most commonly due to failure of meeting the inclusion criteria (n=712) and pertaining to: lack of identification of PIK3CA mutation status (n=372); adequate formalin-fixed paraffin-embedded (FFPE) tumor tissue for analysis of PIK3CA status (n=128); no adequate bone marrow and organ function (n=92); no measurable disease (n=44); patient amendable for curative therapy (n=35).

Table 27: Subject disposition (FAS, PIK3CA mutant cohort) - Study C2301

	Alpelisib + fulvestrant N=169 n (%)	Placebo + fulvestrant N=172 n (%)	All subjects N=341 n (%)
Subjects randomized			
Treated	169 (100)	171(99.4)	340 (99.7)
Untreated	0	1 (0.6)	1 (0.3)
Subjects treated			
Treatment ongoing[1]	42 (24.9)	32 (18.6)	74 (21.7)
End of treatment	127 (75.1)	139 (80.8)	266 (78.0)
Reason for not being treated			
Protocol deviation	0	1 (0.6)	1 (0.3)
Primary reason for end of treatment			
Progressive disease	93 (55.0)	117 (68.0)	210 (61.6)
Subject/guardian decision	16 (9.5)	6 (3.5)	22 (6.5)
Physician decision	6 (3.6)	6 (3.5)	12 (3.5)
Adverse event	5 (3.0)	3 (1.7)	8 (2.3)
Death	3 (1.8)	4 (2.3)	7 (2.1)
Protocol deviation	4 (2.4)	3 (1.7)	7 (2.1)
Post-treatment follow-up phase			
Not applicable[2]	117 (69.2)	135 (78.5)	252 (73.9)
Subjects no longer being followed for post-treatment follow-up	7 (4.1)	5 (2.9)	12 (3.5)
Subjects continuing to be followed for post-treatment follow-up	3 (1.8)	0	3 (0.9)
Primary reason for post-treatment follow-up discontinuation			
Progressive disease	4 (2.4)	1 (0.6)	5 (1.5)
Subject/guardian decision	2 (1.2)	2 (1.2)	4 (1.2)
Death	0	2 (1.2)	2 (0.6)
Physician decision	1 (0.6)	0	1 (0.3)

Percentage was based on N
[1]Subjects ongoing at the time of the data cut-off date
[2]Subjects who discontinued due to progressive disease at the end-of-treatment evaluation, or who did not

Table 28: Subject disposition (FAS, PIK3CA non-mutant cohort) - Study C2301

Disposition reason	Alpelisib + fulvestrant N=115 n (%)	Placebo + fulvestrant N=116 n (%)	All subjects N=231 n (%)
Subjects randomized			
Treated	115 (100)	116 (100)	231 (100)
Subjects treated			
Treatment ongoing[1]	13 (11.3)	14 (12.1)	27 (11.7)
End of treatment	102 (88.7)	102 (87.9)	204 (88.3)
Primary reason for end of treatment			
Progressive disease	80 (69.6)	91 (78.4)	171 (74.0)
Subject/guardian decision	6 (5.2)	4 (3.4)	10 (4.3)
Adverse event	9 (7.8)	0	9 (3.9)
Physician decision	5 (4.3)	4 (3.4)	9 (3.9)
Protocol deviation	1 (0.9)	3 (2.6)	4 (1.7)
Death	1 (0.9)	0	1 (0.4)
Post-treatment follow-up phase			
Not applicable[2]	93 (80.9)	99 (85.3)	192 (83.1)
Subjects no longer being followed for post-treatment follow-up	6 (5.2)	3 (2.6)	9 (3.9)
Subjects continuing to be followed for post-treatment follow-up	3 (2.6)	0	3 (1.3)
Primary reason for post-treatment follow-up discontinuation			
Progressive disease	6 (5.2)	3 (2.6)	9 (3.9)

[1]Subjects ongoing at the time of the data cut-off date
[2]Subjects who discontinued due to progressive disease at the end-of-treatment evaluation, or who did not continue into the next phase, or who continued into the survival follow-up after the end-of-treatment evaluation.
Percentage is based on N.
Reason for not being treated is from eCRF completion page.

Recruitment

Study initiation: 23-Jul-2015 (first subject first visit)

Study completion date: Study ongoing (data cut-off date for efficacy analysis in PIK3CA mutant cohort and safety for both cohorts is 12-Jun-2018, data cut-off for efficacy analysis in PIK3CA non-mutant cohort is 23-Dec-2016).

Conduct of the study

Protocol amendments

The study protocol was amended four times.

Amendment 1 (09-Mar-2016 / 92 subjects randomized) was instituted to modify the assessment of the PIK3CA non-mutant cohort to be a secondary, proof-of-concept objective, based on incoming data from a Phase 1 alpelisib study and Phase 3 buparlisib indicating that a PIK3CA mutant patient may derive greater benefit from a PI3K inhibitor than a patient who is PIK3CA non-mutant. It also slightly restricted inclusion criteria related to basal plasma glucose levels.

Amendment 2 (30-Aug-2016 / 317 subjects randomized) excluded from enrolment subjects relapsed ≥ 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic

disease). Again, inclusion criteria were revised in order to further restrict the recruitment of patients with potential hyperglycemic risk.

Amendment 3 (14-Dec-2016 / 443 randomized) corrected minor issues related to interim analysis and Novartis personnel blinding.

Amendment 4 (22-Nov-2017 / randomization completed) modified guidance for management of skin and subcutaneous reactions.

Another relevant point of amendment 1 (and also of amendment 2) was the modification of inclusion criteria in order to make the trial more restrictive for patients with a trend towards hyperglycemic complications.

Protocol deviations

Overall, 52.5% of subjects in the PIK3CA mutant cohort had at least one protocol deviation (although only a fraction of these warranted exclusion from the PPS – see below). The proportion of subjects with protocol deviations (of any nature) was balanced across the two treatment arms (54.4% in the alpelisib plus fulvestrant arm and 50.6% in the placebo plus fulvestrant arm).

Table 29: Protocol deviations by deviation category (in greater than 5 percent of subjects in either treatment arm) (FAS, PIK3CA mutant cohort) - Study C2301

Category	Alpelisib + fulvestrant N=169 n (%)	Placebo + fulvestrant N=172 n (%)	All subjects N=341 n (%)
Any protocol deviation	**92 (54.4)**	**87 (50.6)**	**179 (52.5)**
Any inclusion criteria deviation	**50 (29.6)**	**55 (32.0)**	**105 (30.8)**
Pat. relapsed on/or within 12 months from completion of (neo)adj. endocrine therapy (ET) and subsequently progressed after 1 line of ET or progressed on more than 1 line of ET for metastatic disease.	16 (9.5)	15 (8.7)	31 (9.1)
No ECG triplicate at Screening.	13 (7.7)	13 (7.6)	26 (7.6)
Baseline laboratory results criteria (creatinine clearance) missing.	5 (3.0)	11 (6.4)	16 (4.7)
Baseline laboratory results criteria (fasting serum amylase) missing.	6 (3.6)	10 (5.8)	16 (4.7)
Prohibited concomitant medication	**35 (20.7)**	**24 (14.0)**	**59 (17.3)**
Other deviation	**13 (7.7)**	**15 (8.7)**	**28 (8.2)**
Patient has not provided consent for the optional biopsy sample collected.	4 (2.4)	9 (5.2)	13 (3.8)
Any exclusion criteria deviation	**11 (6.5)**	**16 (9.3)**	**27 (7.9)**
Subject not withdrawn as per protocol	**13 (7.7)**	**9 (5.2)**	**22 (6.5)**
Study treatment discontinued but patient not withdrawn from treatment phase	9 (5.3)	8 (4.7)	17 (5.0)

Baseline data

Table 30: Demographic and baseline characteristics (Full Analysis Set, PIK3CA mutant cohort) - Study C2301

Demographic variable	Alpelisib plus fulvestrant N=169	Placebo plus fulvestrant N=172	All subjects N=341
Age (years)			
n	169	172	341
Mean (SD)	62.7 (10.22)	64.0 (9.99)	63.3 (10.11)
Median	63.0	64.0	63.0
Min-Max	25 – 87	38 - 92	25 - 92
Age category (years) - n (%)			
18 to < 65	95 (56.2)	89 (51.7)	184 (54.0)
65 to < 85	73 (43.2)	80 (46.5)	153 (44.9)
≥ 85	1 (0.6)	3 (1.7)	4 (1.2)
Sex - n (%)			
Female	168 (99.4)	172 (100)	340 (99.7)
Male	1 (0.6)	0	1 (0.3)
Race - n (%)			
White	117 (69.2)	109 (63.4)	226 (66.3)
Asian	34 (20.1)	40 (23.3)	74 (21.7)
Other	8 (4.7)	10 (5.8)	18 (5.3)
Unknown	8 (4.7)	8 (4.7)	16 (4.7)
Black or African American	1 (0.6)	3 (1.7)	4 (1.2)
American Indian or Alaska Native	1 (0.6)	2 (1.2)	3 (0.9)
Ethnicity - n (%)			
Other	66 (39.1)	65 (37.8)	131 (38.4)
East Asian	27 (16.0)	34 (19.8)	61 (17.9)
Hispanic or Latino	21 (12.4)	27 (15.7)	48 (14.1)
Not reported	24 (14.2)	19 (11.0)	43 (12.6)
Unknown	15 (8.9)	13 (7.6)	28 (8.2)
Russian	5 (3.0)	6 (3.5)	11 (3.2)
South Asian	3 (1.8)	3 (1.7)	6 (1.8)
West Asian	4 (2.4)	2 (1.2)	6 (1.8)
Southeast Asian	2 (1.2)	2 (1.2)	4 (1.2)
Mixed ethnicity	2 (1.2)	1 (0.6)	3 (0.9)
Body mass index (kg/m^2)			
n	169	171	340
Mean (SD)	27.2 (5.62)	27.0 (5.77)	27.1 (5.69)
Median	26.5	26.1	26.4
Min-Max	15 - 46	17 - 52	15 - 52
ECOG performance status - n (%)			
0	112 (66.3)	113 (65.7)	225 (66.0)
1	56 (33.1)	58 (33.7)	114 (33.4)
Missing[1]	1 (0.6)	1 (0.6)	2 (0.6)

Body mass index: BMI [kg/m2] = weight[kg]/(height [m]^2)
[1] ECOG was missing because it was collected after start of treatment and not during screening

Source: [Study C2301-Table 14.1-3.1a]

Table 31: Diagnosis and extent of cancer (Full Analysis Set, PIK3CA mutant cohort) – Study C2301

Disease history	Alpelisib plus fulvestrant N=169 n (%)	Placebo plus fulvestrant N=172 n (%)	All subjects N=341 n (%)
Primary site of cancer – n (%)			
Breast	169 (100)	172 (100)	341 (100)
Details of tumor histology/cytology – n (%)			
Invasive ductal carcinoma	115 (68.0)	98 (57.0)	213 (62.5)
Invasive lobular carcinoma	22 (13.0)	26 (15.1)	48 (14.1)
Adenocarcinoma	15 (8.9)	24 (14.0)	39 (11.4)
Papillary serous	0	2 (1.2)	2 (0.6)
Papillary	0	2 (1.2)	2 (0.6)
Ductal carcinoma in situ	1 (0.6)	0	1 (0.3)
Undifferentiated carcinoma	1 (0.6)	0	1 (0.3)
Inflammatory carcinoma	1 (0.6)	0	1 (0.3)
Lobular carcinoma in situ	1 (0.6)	0	1 (0.3)
Other	13 (7.7)	14 (8.1)	27 (7.9)
Not applicable	0	6 (3.5)	6 (1.8)
Histologic grade – n (%)			
Well differentiated	23 (13.6)	20 (11.6)	43 (12.6)
Moderately differentiated	83 (49.1)	77 (44.8)	160 (46.9)
Poorly differentiated	46 (27.2)	40 (23.3)	86 (25.2)
Undifferentiated	1 (0.6)	4 (2.3)	5 (1.5)
Unknown[1]	16 (9.5)	31 (18.0)	47 (13.8)
Stage at initial diagnosis – n (%)			
0	1 (0.6)	0	1 (0.3)
I	21 (12.4)	21 (12.2)	42 (12.3)
II	67 (39.6)	73 (42.4)	140 (41.1)
III	42 (24.9)	50 (29.1)	92 (27.0)
IV	35 (20.7)	25 (14.5)	60 (17.6)
Unknown	1 (0.6)	0	1 (0.3)
Missing	2 (1.2)	3 (1.7)	5 (1.5)
Stage at time of study entry – n (%)			
III	1 (0.6)	7 (4.1)	8 (2.3)
IV	168 (99.4)	165 (95.9)	333 (97.7)
Time since initial diagnosis of primary site (months)			
<6	1 (0.6)	0	1 (0.3)
≥ 6	168 (99.4)	172 (100)	340 (99.7)
Time since initial diagnosis of primary site (months)			
n	169	172	341
Mean (SD)	84.0 (66.44)	79.5 (65.49)	81.7 (65.91)
Median (range)	65.6 (5.3 - 378.2)	62.4 (7.5 - 399.8)	64.0 (5.3 - 399.8)
Time from initial diagnosis to first recurrence/progression (months)			
n	169	172	341
Mean (SD)	69.8 (57.43)	65.3 (56.17)	67.5 (56.76)
Median (range)	56.6 (0.4 - 343.2)	50.7 (1.1 - 390.1)	53.7 (0.4 - 390.1)
Time since most recent relapse/ progression (months) if last treatment was neo-adjuvant – n (%)			
<12 months	79 (46.7)	78 (45.3)	157 (46.0)
Time since most recent relapse/ progression (months) if last treatment was neo-adjuvant			
n	79	78	157
Mean (SD)	1.8 (1.22)	1.8 (1.27)	1.8 (1.24)
Median (range)	1.6	1.6	1.6
Min- Max	0.5 - 9.2	0.6 - 10.1	0.5 – 10.1

Disease history	Alpelisib plus fulvestrant N=169 n (%)	Placebo plus fulvestrant N=172 n (%)	All subjects N=341 n (%)
Time since most recent relapse/ progression (months) if last treatment was for advanced disease – n (%)			
>3 months	15 (8.9)	10 (5.8)	25 (7.3)
1 to ≤ 3 months	49 (29.0)	67 (39.0)	116 (34.0)
<1 months	25 (14.8)	15 (8.7)	40 (11.7)
Unknown	0	1 (0.6)	1 (0.3)
Time since most recent relapse/ progression (months) if last treatment was for advanced disease			
n	89	92	181
Mean (SD)	1.8 (1.23)	1.8 (0.92)	1.8 (1.08)
Median (range)	1.4 (0.1 – 8.3)	1.6 (0.5 – 5.0)	1.5 (0.1 – 8.3)
Types of lesions at baseline – n (%)			
Target only	19 (11.2)	17 (9.9)	36 (10.6)
Non-target only	43 (25.4)	36 (20.9)	79 (23.2)
Both target and non-target	107 (63.3)	119 (69.2)	226 (66.3)
Current extent of disease (metastatic sites) – n (%)			
Bone	131 (77.5)	121 (70.3)	252 (73.9)
Bone only	42 (24.9)	35 (20.3)	77 (22.6)
Visceral	93 (55.0)	100 (58.1)	193 (56.6)
Lung	57 (33.7)	68 (39.5)	125 (36.7)
Liver	49 (29.0)	54 (31.4)	103 (30.2)
Other visceral	3 (1.8)	1 (0.6)	4 (1.2)
Lymph nodes	56 (33.1)	65 (37.8)	121 (35.5)
Skin	4 (2.4)	6 (3.5)	10 (2.9)
Breast	1 (0.6)	3 (1.7)	4 (1.2)
CNS	0	2 (1.2)	2 (0.6)
None	0	1 (0.6)	1 (0.3)
Other	25 (14.8)	18 (10.5)	43 (12.6)
Number of metastatic sites involved – n (%)			
0	0	1 (0.6)	1 (0.3)
1	63 (37.3)	52 (30.2)	115 (33.7)
2	58 (34.3)	60 (34.9)	118 (34.6)
3	24 (14.2)	42 (24.4)	66 (19.4)
4	19 (11.2)	10 (5.8)	29 (8.5)
≥ 5	5 (3.0)	7 (4.1)	12 (3.5)
HER2 receptor status – n (%)			
Negative	169 (100)	172 (100)	341 (100)
Estrogen receptor status – n (%)			
Positive	167 (98.8)	172 (100)	339 (99.4)
Negative	2 (1.2)	0	2 (0.6)
Progesterone receptor status – n (%)			
Positive	120 (71.0)	132 (76.7)	252 (73.9)
Negative	46 (27.2)	38 (22.1)	84 (24.6)
Unknown	3 (1.8)	2 (1.2)	5 (1.5)
Estrogen and/or progesterone receptor status – n (%)			
At least one positive	169 (100)	172 (100)	341 (100)
Both positive	118 (69.8)	132 (76.7)	250 (73.3)

[1] Included subjects with histological grade performed with unknown result

Source: [Study C2301-Table 14.1-3.2a]

Table 32: Prior antineoplastic therapy (Full Analysis Set, PIK3CA mutant cohort) – Study C2301

Characteristic	Alpelisib plus fulvestrant N=169 n (%)	Placebo plus fulvestrant N=172 n (%)	All subjects N=341 n (%)
Any therapy			
Yes	169 (100)	172 (100)	341 (100)
Surgery			
Yes	147 (87.0)	151 (87.8)	298 (87.4)
No	22 (13.0)	21 (12.2)	43 (12.6)
Radiotherapy			
Yes	118 (69.8)	128 (74.4)	246 (72.1)
No	51 (30.2)	44 (25.6)	95 (27.9)
Medication: chemotherapy setting[1]			
None	68 (40.2)	65 (37.8)	133 (39.0)
Adjuvant	78 (46.2)	86 (50.0)	164 (48.1)
Neoadjuvant	25 (14.8)	29 (16.9)	54 (15.8)
Therapeutic	0	1 (0.6)	1 (0.3)
Medication: other therapy setting[1]			
Adjuvant	125 (74.0)	126 (73.3)	251 (73.6)
Neoadjuvant	4 (2.4)	3 (1.7)	7 (2.1)
Palliative	1 (0.6)	0	1 (0.3)
Therapeutic	81 (47.9)	83 (48.3)	164 (48.1)
Type of last therapy			
Chemotherapy	0	1 (0.6)	1 (0.3)
Hormonal therapy	116 (68.6)	115 (66.9)	231 (67.7)
Targeted therapy	5 (3.0)	4 (2.3)	9 (2.6)
Radiotherapy	45 (26.6)	43 (25.0)	88 (25.8)
Surgery	9 (5.3)	14 (8.1)	23 (6.7)
Other	2 (1.2)	1 (0.6)	3 (0.9)
Setting at last therapy			
Adjuvant	75 (44.4)	73 (42.4)	148 (43.4)
Palliative	24 (14.2)	25 (14.5)	49 (14.4)
Therapeutic	62 (36.7)	60 (34.9)	122 (35.8)
Not applicable	9 (5.3)	14 (8.1)	23 (6.7)
Other	1 (0.6)	1 (0.6)	2 (0.6)
Best response to last therapy			
Complete response (CR)	1 (0.6)	0	1 (0.3)
Partial response (PR)	19 (11.2)	12 (7.0)	31 (9.1)
Stable disease (SD)	33 (19.5)	35 (20.3)	68 (19.9)
Progressive disease (PD)	47 (27.8)	47 (27.3)	94 (27.6)
Non-CR/Non-PD	0	2 (1.2)	2 (0.6)
Unknown	4 (2.4)	5 (2.9)	9 (2.6)
Not applicable[2]	70 (41.4)	74 (43.0)	144 (42.2)

[1] A subject might have had multiple settings. Last therapy started prior to randomization. Setting and best response at last therapy will be set to 'Not applicable' if the type of last therapy is surgery (non-biopsy procedures).
[2] Best response at last therapy will be set to 'Not applicable' if the type of the last therapy is radiotherapy

Source: [Study C2301-Table 14.1-4.1a]

Table 33: Characteristics of last prior hormonal therapy (Full Analysis Set, PIK3CA mutant cohort) – Study C2301

Characteristics of last hormonal therapy	Alpelisib plus fulvestrant N=169 n (%)	Placebo plus fulvestrant N=172 n (%)	All subjects N=341 n (%)
Aromatase inhibitors	**165 (97.6)**	**168 (97.7)**	**333 (97.7)**
Letrozole	99 (58.6)	94 (54.7)	193 (56.6)
Anastrozole	54 (32.0)	65 (37.8)	119 (34.9)
Exemestane	20 (11.8)	19 (11.0)	39 (11.4)
Anti-estrogen therapy	**25 (14.8)**	**29 (16.9)**	**54 (15.8)**
Tamoxifen	23 (13.6)	29 (16.9)	52 (15.2)
Fulvestrant	1 (0.6)	0	1 (0.3)
Other	1 (0.6)	0	1 (0.3)
Setting at last hormonal therapy	**169 (100)**	**172 (100)**	**341 (100)**
Adjuvant	88 (52.1)	89 (51.7)	177 (51.9)
Neoadjuvant	2 (1.2)	2 (1.2)	4 (1.2)
Palliative	1 (0.6)	0	1 (0.3)
Therapeutic	80 (47.3)	83 (48.3)	163 (47.8)
Primary endocrine resistance	23 (13.6)	22 (12.8)	45 (13.2)
Secondary endocrine resistance	120 (71.0)	127 (73.8)	247 (72.4)
Endocrine sensitivity	20 (11.8)	19 (11.0)	39 (11.4)
BOR at last hormonal therapy in metastatic setting	80 (47.3)	83 (48.3)	163 (47.8)
Complete response (CR)	1 (0.6)	1 (0.6)	2 (0.6)
Partial response (PR)	20 (11.8)	16 (9.3)	36 (10.6)
Stable disease with duration < 24 weeks[4]	4 (2.4)	3 (1.7)	7 (2.1)
Stable disease with duration ≥ 24 weeks[4]	41 (24.3)	45 (26.2)	86 (25.2)
Progressive disease (PD)	8 (4.7)	9 (5.2)	17 (5.0)
Non-CR/Non-PD	0	4 (2.3)	4 (1.2)
Unknown	6 (3.6)	6 (3.5)	12 (3.5)

Last hormonal therapy refers to hormonal medication received in the last regimen.
Percentages based on N
Primary and secondary resistance as per ESMO definition.
[1] Relapse <24 months while on ET in adjuvant setting or progression < 6 months while on ET in metastatic setting
[2] Relapse ≥ 24 months while on ET in adjuvant setting or relapse <12 months after end of ET in adjuvant setting or progression ≥ 6 months while on ET in metastatic setting
[3] Relapse ≥ 12 months after end ET in adjuvant setting or progression ≥ 12 months after end of ET in metastatic setting
[4] If multiple hormonal therapy medications are given as part of last regimen, then duration of treatment is derived as the time from the earliest start date to the last end date of all given hormonal therapy medications.

Source: [Study C2301-Table 14.1-4.6a]

Table 34: Duration (months) of last hormonal treatment - Study C2301 (Full Analysis Set)

	PIK3CA mutant cohort		PIK3CA non-mutant cohort	
Setting	**Alpelisib + Fulv N=169**	**Placebo + Fulv N=172**	**Alpelisib + Fulv N=115**	**Placebo + Fulv N=116**
Neo/Adjuvant				
n	88	89	72	62
Mean (SD)	51.5 (28.44)	48.3 (30.40)	40.0 (33.86)	47.3 (32.66)
Median	51.8	41.8	39.2	45.3
Q1-Q3	31.8-61.0	27.4-61.1	15.1-57.9	22.1-60.2
Min-Max	6 - 182	3 - 191	2 - 221	2 - 167
Metastatic				
n	80	82	43	52
Mean (SD)	21.8 (19.06)	23.5 (21.64)	24.3 (22.55)	17.6 (14.41)
Median	15.2	16.2	19.4	14.0
Q1-Q3	9.4-29.0	10.3-27.7	9.3-30.8	7.7-22.3
Min-Max	2 - 104	3 - 114	2 - 113	2 - 69

Q1 and Q3 are the 25th and 75th percentiles

Source: [Table 135-1a], [Table 135-1b]

PIK3CA mutation status

Tumour testing

Study C2301 initiated in July 2015 with PIK3CA mutation testing performed on formalin-fixed, paraffin-embedded (FFPE) tumour biopsy specimens, from either initial diagnosis or the most recent biopsy, utilising the Novartis PIK3CA PCR mutation CTA. On 28 September 2016, when enrolment for the PIK3CA non-mutant cohort was substantially complete, C2301 mutation screening transitioned to the QIAGEN therascreen PIK3CA RGQ PCR Kit, the companion diagnostic (CDx) developed for alpelisib (hereafter referred to as Tissue CDx). Enrollment for the C2301 PIK3CA non-mutant cohort ended on 21 December 2016. Screening continued to identify PIK3CA mutation positive patients for the C2301 mutant cohort until completion of randomization (21 July 2017).

Of the 572 patients randomized in C2301, 395 were enrolled based on PIK3CA mutation status determined using the CTA (CTA-enrolled) and 177 were enrolled based on the Tissue CDx (CDx-enrolled).

Plasma testing

Plasma samples were collected from randomized patients prior to initiation of study treatment and stored until retrospective analysis using the QIAGEN therascreen PIK3CA Plasma RGQ PCR Kit (Plasma CDx).

Numbers analysed

Table 35: Analysis sets and stratum (FAS, PIK3CA mutant cohort)

Analysis set	Alpelisib + fulvestrant N=169 n (%)	Placebo + fulvestrant N=172 n (%)	All subjects N=341 n (%)
Full analysis set	169 (100)	172 (100)	341 (100)
Presence of lung and/or liver metastases	84 (49.7)	86 (50.0)	170 (49.9)
Prior CDK4/6 inhibitor usage	9 (5.3)	11 (6.4)	20 (5.9)
Safety set	169 (100)	171 (100)	340 (100)
Presence of lung and/or liver metastases	84 (49.7)	85 (49.7)	169 (49.7)
Prior CDK4/6 inhibitor usage	9 (5.3)	11 (6.4)	20 (5.9)
Per-protocol set	144 (85.2)	148 (86.0)	292 (85.6)
Presence of lung and/or liver metastases	74 (43.8)	77 (44.8)	151 (44.3)
Prior CDK4/6 inhibitor usage	8 (4.7)	10 (5.8)	18 (5.3)
Pharmacokinetic analysis set	159 (94.1)	133 (77.8)	292 (85.9)

N is the number of subjects in the Full analysis set.
Full analysis set included all subjects who were randomized to study treatment
Safety set included all subjects who were randomized to study treatment and received at least one dose of study treatment (either fulvestrant or alpelisib/placebo)
Per-protocol set included all subjects in the FAS who did not have any protocol deviations that could confound the interpretation of the primary analyses conducted on the FAS.
Pharmacokinetic analysis set included all subjects who received at least one dose of study treatment (alpelisib/placebo or fulvestrant) and had at least one post-treatment concentration measurement. Percentages for PAS were calculated using the Safety set as denominator.
Source: Table 14.1-2.1a

Table 36: Analysis sets and stratum (FAS, PIK3CA non-mutant cohort)

	Alpelisib + fulvestrant N=115 n (%)	Placebo + fulvestrant N=116 n (%)	All Subjects N=231 n (%)
Full analysis set	**115 (100)**	**116 (100)**	**231 (100)**
Presence of lung and/or liver metastases	56 (48.7)	56 (48.3)	112 (48.5)
Prior CDK4/6 inhibitor usage	7 (6.1)	8 (6.9)	15 (6.5)
Safety set	**115 (100)**	**116 (100)**	**231 (100)**
Presence of lung and/or liver metastases	56 (48.7)	56 (48.3)	112 (48.5)
Prior CDK4/6 inhibitor usage	7 (6.1)	8 (6.9)	15 (6.5)
Pharmacokinetic analysis set	**114 (99.1)**	**115 (99.1)**	**229 (99.1)**

N is the number of subjects in the full analysis set
Full analysis set included all subjects who were randomized to study treatment
Safety set included all subjects who were randomized to study treatment and received at least one dose of study treatment (either fulvestrant or alpelisib/placebo)
Pharmacokinetic analysis set included all subjects who received at least one dose of study treatment (alpelisib/placebo or fulvestrant) and had at least one post-treatment concentration measurement. Percentages for PAS were calculated using the Safety set as denominator.
Source: Table 14.1-2.1b

Outcomes and estimation

Primary Efficacy Variable: PFS in the PIK3CA mutant cohort

The PFS analysis was final and based on 232 events and a median follow-up time of 20.2 months corresponding to 61% events in the alpelisib arm (DCO 12 June 2018).

The efficacy results in the cohort with PIK3CA mutation demonstrated a statistically significant improvement in PFS in patients receiving alpelisib plus fulvestrant, compared to patients receiving placebo plus fulvestrant with an estimated 35% risk reduction of disease progression or death (HR = 0.65; 95% CI: 0.50, 0.85; stratified log-rank test p = 0.00065, one-sided).

Median PFS was prolonged by 5.3 months, i.e. from 5.7 months (95% CI: 3.7 - 7.4) for the placebo plus fulvestrant arm to 11.0 months (95% CI: 7.5, 14.5) for the alpelisib plus fulvestrant arm

The estimated Kaplan-Meier PFS rates at 12 months were 46.2% (95% CI: 38.1, 54.0) in the alpelisib plus fulvestrant arm and 32.9% (95% CI: 25.8, 40.2) in the placebo plus fulvestrant arm.

Table 37: Analysis of PFS per investigator review (Full Analysis Set, PIK3CA mutant cohort) – Study C2301 (DCO 12 June 2018)

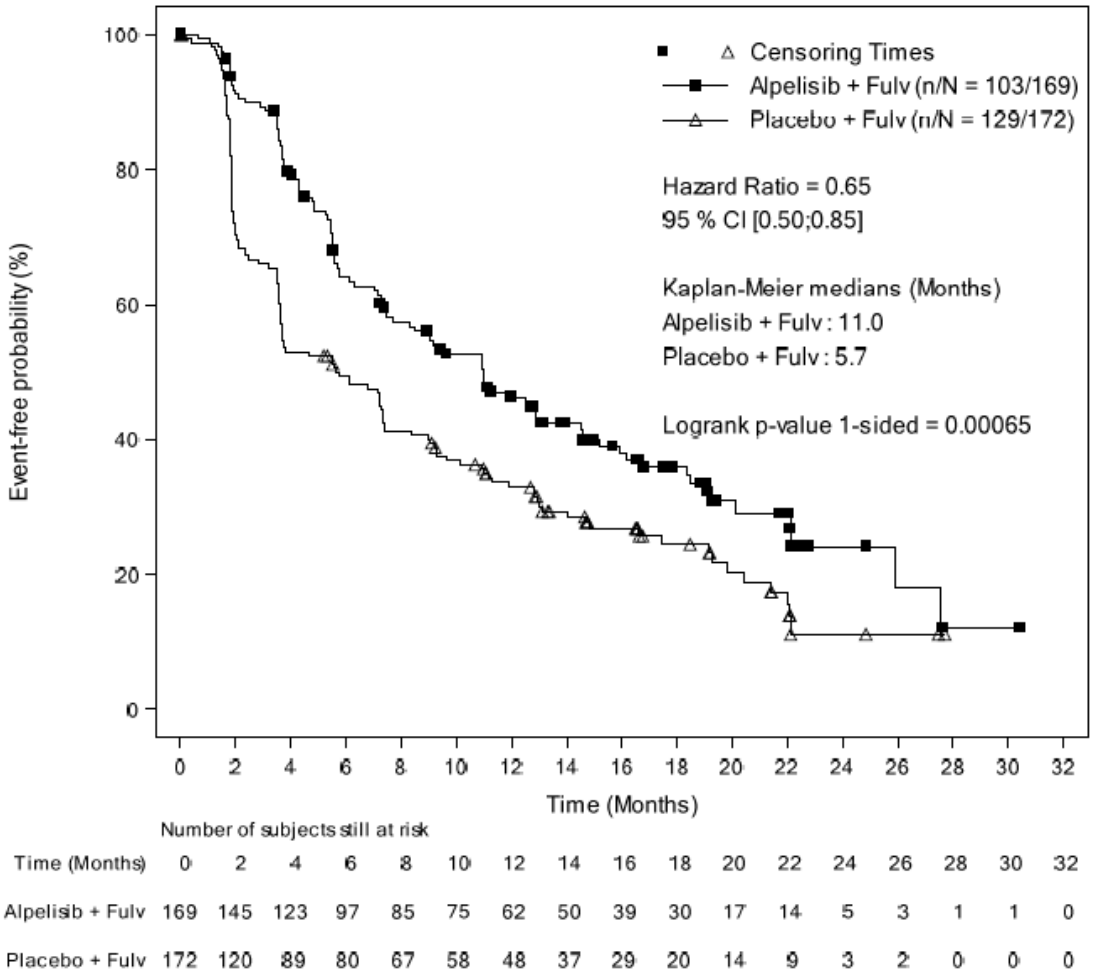
		Stratified log-rank test		Stratified Cox model	
	Events/N (%)	Median time (95% CI) (months)[3]	p-value[4]	Hazard ratio[5]	95% CI
All subjects[1]					
Alpelisib arm	103/169 (60.9)	11.0 (7.49, 14.52)	0.00065	0.65	(0.50, 0.85)
Placebo arm	129/172 (75.0)	5.7 (3.65, 7.36)			
Presence of liver/lung metastases[2]					
Alpelisib arm	53/84 (63.1)	9.0 (5.55, 14.52)	NA	0.62	(0.44, 0.89)
Placebo arm	72/86 (83.7)	3.7 (2.86, 6.11)			
Absence of liver/lung metastases[2]					
Alpelisib arm	50/85 (58.8)	11.0 (8.31, 19.12)	NA	0.69	(0.47, 1.01)
Placebo arm	57/86 (66.3)	9.0 (3.65, 11.17)			
Prior CDK4/6 inhibitor use[2]					
Alpelisib arm	7/9 (77.8)	5.5 (1.58, 16.76)	NA	0.48	(0.17, 1.36)
Placebo arm	10/11 (90.9)	1.8 (1.68, 3.58)			
No prior CDK4/6 inhibitor use[2]					
Alpelisib arm	96/160 (60.0)	11.0 (8.31, 14.55)	NA	0.67	(0.51, 0.87)
Placebo arm	119/161 (73.9)	6.8 (3.68, 9.00)			

[1] Both log-rank test and Cox PH model are stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases.
[2] Within each stratum, Cox PH model is stratified by other strata within study (prior CDK4/6 inhibitor use - stratified by presence of lung/liver metastases; presence of lung/liver metastases stratified by prior CDK4/6 inhibitor use).
[3] Median (time to event) and its 95% CI are generated by KM estimation.
[4] P-value is one-tailed and calculated for 'All subjects' group. It will be compared to pre-specified significance level defined by the study.
[5] Hazard ratio of alpelisib plus fulvestrant vs. placebo plus fulvestrant (placebo plus fulvestrant is the control).
NA: Not applicable Source: [Study C2301-Table 14.2-1.1a]

Table 38: Progression-free survival analyses per investigator assessment in subjects with PIK3CA mutant tumours – Study C2301 (FAS) (DCO 12 June 2018)

Progression-free survival [a]	Alpelisib plus fulvestrant N = 169	Placebo plus fulvestrant N = 172
Number of PFS events – n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Number censored – n (%)	66 (39.1)	43 (25.0)
Median PFS (95% confidence interval) [b] – months	11.0 (7.49, 14.52)	5.7 (3.65, 7.36)
Hazard ratio (95% confidence interval) [c]	0.65 (0.50, 0.85)	
p-value	0.00065	

FAS full analysis set, PFS progression-free survival
[a] Both log-rank test and Cox proportional hazards model are stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases. P-value is compared to pre-specified Haybittle-Peto stopping boundary (one-sided $p \leq 0.0199$).
[b] Median (time to event) and its 95% confidence interval are generated by Kaplan-Meier estimation
[c] Hazard ratio of alpelisib plus fulvestrant vs. placebo plus fulvestrant (where placebo + fulvestrant is the control)
Source: [Study C2301-Table 14.2-1.1a], [Study C2301-Table 14.2-1.3a]



Number of subjects still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Alpelisib + Fulv	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo + Fulv	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

Source: [Study C2301-Figure 14.2-1.1a]

Stratified Log rank test and stratified Cox model using strata defined by (i) prior CDK4/6 inhibitor use, (ii) presence of liver and/or lung metastases.

Figure 25: Kaplan-Meier plot of PFS per investigator assessment (Full Analysis Set, PIK3CA mutant cohort) – Study C2301 (DCO 12 June 2018)

Table 39: Reasons for censoring subjects in PFS analysis per Investigator (FAS, PIK3CA mutant cohort) (DCO 12 June 2018)

Reason for censoring	Alpelisib + fulvestrant N=169 n (%)	Placebo+fulvestrant N=172 n (%)
Number of subjects censored	66 (39.1)	43 (25.0)
Reason for censoring		
Ongoing without event[1]	45 (26.6)	31 (18.0)
Withdrew consent	10 (5.9)	5 (2.9)
Event documented after two or more missing tumor assessments	3 (1.8)	1 (0.6)
Adequate assessment no longer available[2]	8 (4.7)	6 (3.5)

[1]Subjects without an event and who had adequate follow-up as of data cut-off
[2]Subjects censored without adequate evaluations for a specified period prior to data cut-off or without adequate baseline assessment
Source: Table 14.2-1.4a

Table 40: Overview of sensitivity analyses of PFS per Investigator (FAS, PIK3CA mutant cohort) (DCO 12 June 2018)

Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)[4]
FAS			
Alpelisib plus fulvestrant	11.0 (7.49,14.52)	0.00065	0.65 (0.50, 0.85)
Placebo plus fulvestrant	5.7 (3.65,7.36)		
Actual event approach [1]			
Alpelisib plus fulvestrant	10.9 (7.49, 12.94)	0.0009	0.66 (0.51, 0.86)
Placebo plus fulvestrant	5.7 (3.65, 7.36)		
Backdating approach[2]			
Alpelisib plus fulvestrant	10.9 (7.43, 12.88)	0.0009	0.66 (0.51, 0.86)
Placebo plus fulvestrant	5.5 (3.65, 7.36)		
Unstratified log-rank test and Cox model			
Alpelisib plus fulvestrant	11.0 (7.49, 14.52)	0.0004	0.64 (0.49, 0.83)
Placebo plus fulvestrant	5.7 (3.65, 7.36)		
Censoring subjects after new antineoplastic therapy[3]			
Alpelisib plus fulvestrant	11.0 (7.72, 14.52)	0.0009	0.66 (0.51, 0.86)
Placebo plus fulvestrant	5.7 (3.65, 7.39)		

[1]Analysis included the event whenever it occurred even after ≥ 2 missing tumor assessments
[2]Analysis used the date of the next scheduled assessment for events occurring after ≥ 1 missing assessment
[3]Analysis was performed by censoring subjects at start of new antineoplastic therapy
[4]Hazard Ratio of alpelisib plus fulvestrant vs. placebo plus fulvestrant (placebo plus fulvestrant is the control) p-values made no adjustment for multiple testing
Source: Table 14.2-1.1a, Table 14.2-1.6a, Table 14.2-1.7a, Table 14.2-1.8a, Table 14.2-1.10a

Results from the primary analysis were confirmed by the central review of radiological response performed in half the population in an audit approach assessment. An estimated 52% risk reduction in disease progression or death was observed (HR = 0.48; 95% CI: 0.32, 0.71) in favour of the alpelisib plus fulvestrant arm over the placebo plus fulvestrant arm. The median PFS was prolonged by 7.4

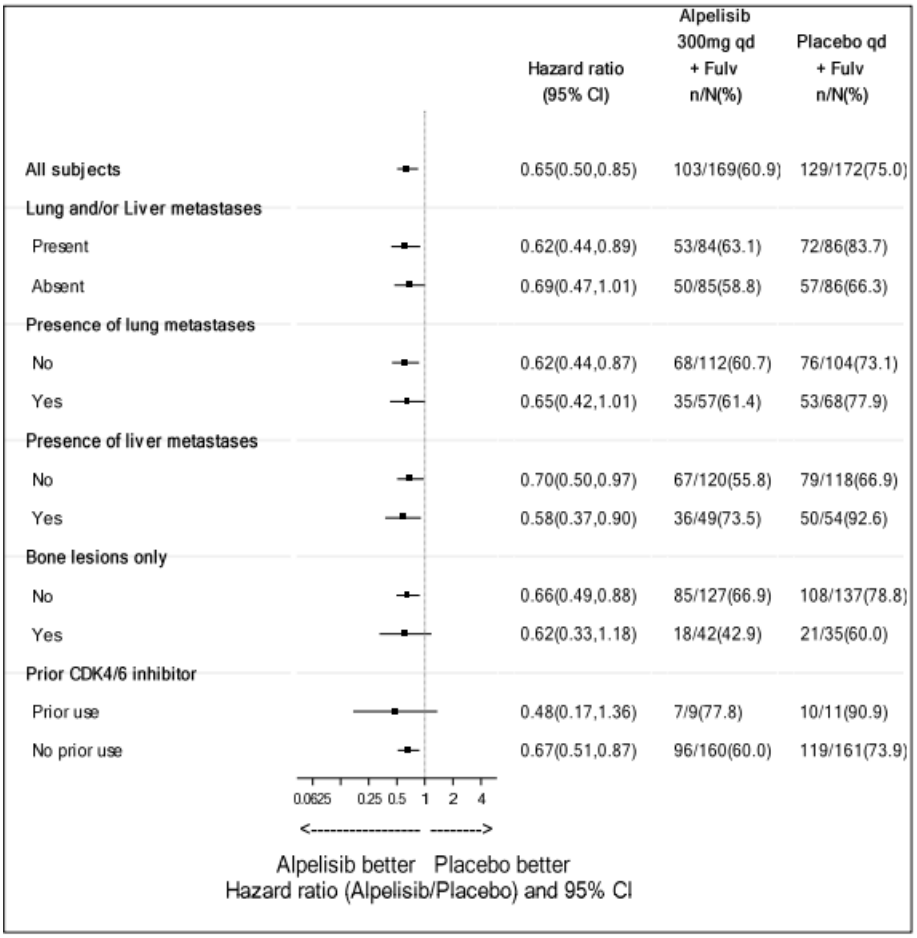
months, from 3.7 months for subjects receiving placebo plus fulvestrant to 11.1 months for the alpelisib plus fulvestrant arm.

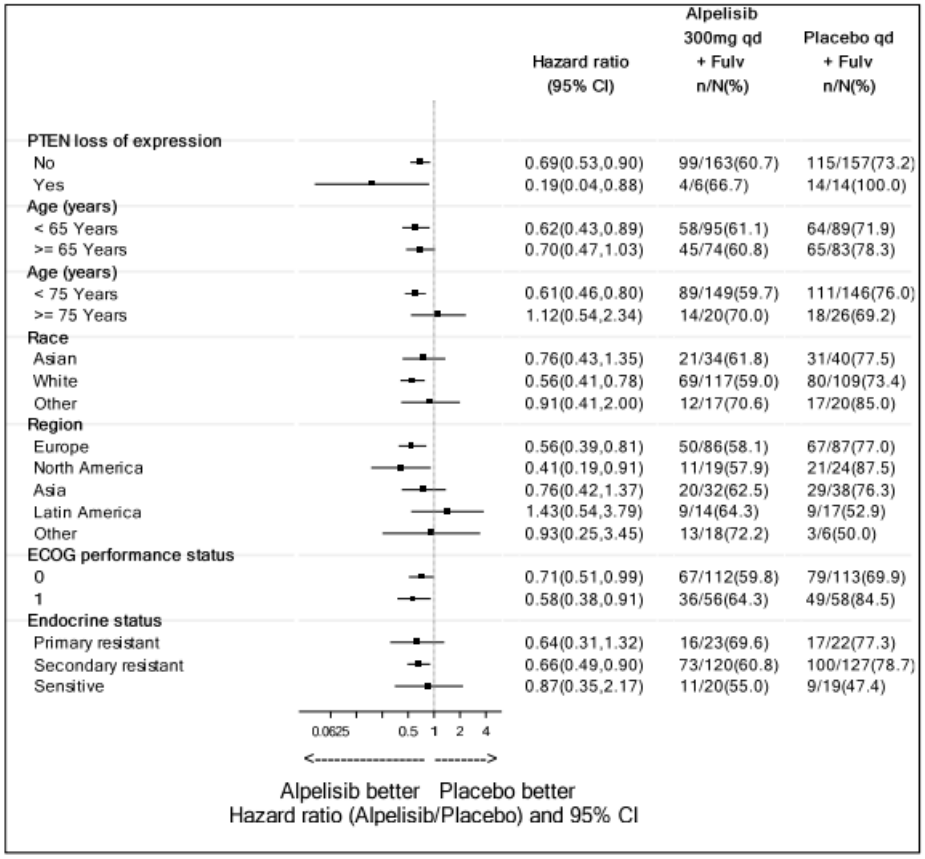
Table 41: Progression-free survival per investigator assessment by stratification factors – Study C2301 (FAS, PIK3CA mutant cohort) (DCO 12 June 2018)

	Hazard ratio (95% CI)	Median PFS (mo) (95% CI)			
		n	Alpelisib plus fulvestrant	n	Placebo plus fulvestrant
All subjects	**0.65 (0.50, 0.85)**	**169**	**11.0 (7.49, 14.52)**	**172**	**5.7 (3.65, 7.36)**
Prior CDK4/6 inhibitor use	0.48 (0.17, 1.36)	9	5.5 (1.58, 16.76)	11	1.8 (1.68, 3.58)
No prior CDK4/6 inhibitor use	0.67 (0.51, 0.87)	160	11.0 (8.31, 14.55)	161	6.8 (3.68, 9.00)
Presence of lung/liver metastases	0.62 (0.44, 0.89)	84	9.0 (5.55, 14.52)	86	3.7 (2.86, 6.11)
Absence of lung/liver metastases	0.69 (0.47, 1.01)	85	11.0 (8.31, 19.12)	86	9.0 (3.65, 11.17)

CDK4/6 cyclin-dependent kinase 4/6, CI confidence interval
Within each stratum, Cox PH model is stratified by other strata (prior CDK4/6 inhibitor use - stratified by presence of lung/liver metastases; Presence of lung/liver metastases stratified by prior CDK4/6 inhibitor use).
Median (time to event) and its 95% CI are generated by KM estimation.
Hazard ratio of alpelisib plus fulvestrant vs. placebo plus fulvestrant (placebo plus fulvestrant is the control)
Source: [Study C2301-Table 14.2-1.1a]

Subgroup analysis of PFS (DCO 12 June 2018)




Hazard ratio (95% CI)
Alpelisib 300mg qd + Fulv n/N(%)
Placebo qd + Fulv n/N(%)
PTEN loss of expression
No 0.69(0.53,0.90) 99/163(60.7) 115/157(73.2)
Yes 0.19(0.04,0.88) 4/6(66.7) 14/14(100.0)
Age (years)
< 65 Years 0.62(0.43,0.89) 58/95(61.1) 64/89(71.9)
>= 65 Years 0.70(0.47,1.03) 45/74(60.8) 65/83(78.3)
Age (years)
< 75 Years 0.61(0.46,0.80) 89/149(59.7) 111/146(76.0)
>= 75 Years 1.12(0.54,2.34) 14/20(70.0) 18/26(69.2)
Race
Asian 0.76(0.43,1.35) 21/34(61.8) 31/40(77.5)
White 0.56(0.41,0.78) 69/117(59.0) 80/109(73.4)
Other 0.91(0.41,2.00) 12/17(70.6) 17/20(85.0)
Region
Europe 0.56(0.39,0.81) 50/86(58.1) 67/87(77.0)
North America 0.41(0.19,0.91) 11/19(57.9) 21/24(87.5)
Asia 0.76(0.42,1.37) 20/32(62.5) 29/38(76.3)
Latin America 1.43(0.54,3.79) 9/14(64.3) 9/17(52.9)
Other 0.93(0.25,3.45) 13/18(72.2) 3/6(50.0)
ECOG performance status
0 0.71(0.51,0.99) 67/112(59.8) 79/113(69.9)
1 0.58(0.38,0.91) 36/56(64.3) 49/58(84.5)
Endocrine status
Primary resistant 0.64(0.31,1.32) 16/23(69.6) 17/22(77.3)
Secondary resistant 0.66(0.49,0.90) 73/120(60.8) 100/127(78.7)
Sensitive 0.87(0.35,2.17) 11/20(55.0) 9/19(47.4)
0.0625 0.5 1 2 4
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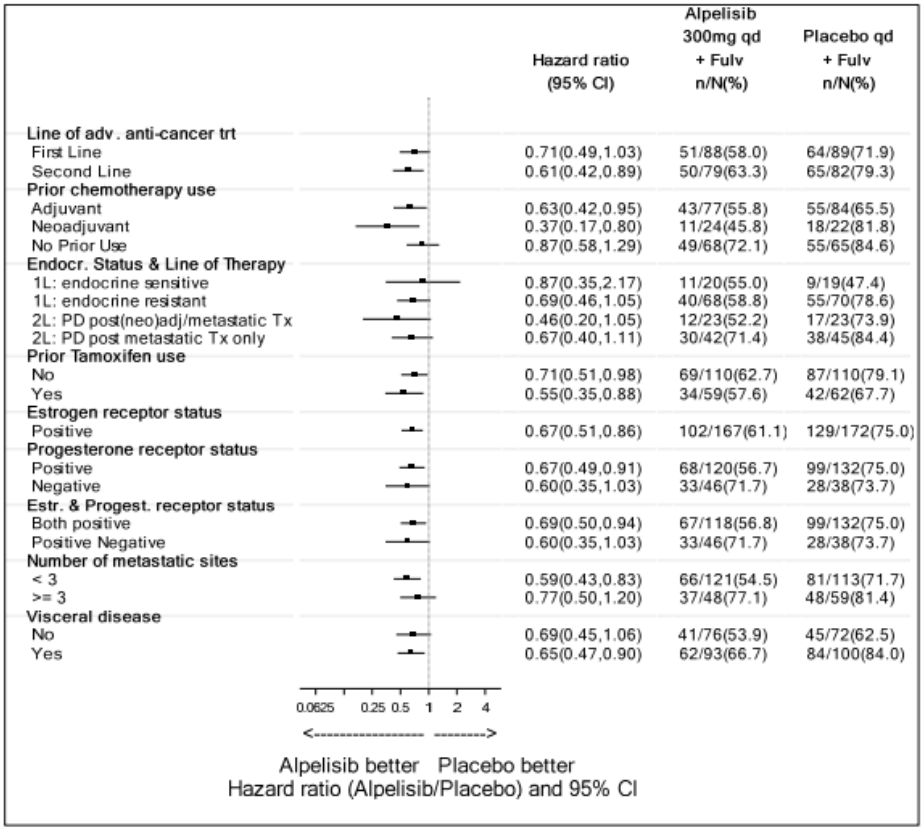
Alpelisib better Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI


Hazard ratio (95% CI)
Alpelisib 300mg qd + Fulv n/N(%)
Placebo qd + Fulv n/N(%)
Line of adv. anti-cancer trt
First Line 0.71(0.49,1.03) 51/88(58.0) 64/89(71.9)
Second Line 0.61(0.42,0.89) 50/79(63.3) 65/82(79.3)
Prior chemotherapy use
Adjuvant 0.63(0.42,0.95) 43/77(55.8) 55/84(65.5)
Neoadjuvant 0.37(0.17,0.80) 11/24(45.8) 18/22(81.8)
No Prior Use 0.87(0.58,1.29) 49/68(72.1) 55/65(84.6)
Endocr. Status & Line of Therapy
1L: endocrine sensitive 0.87(0.35,2.17) 11/20(55.0) 9/19(47.4)
1L: endocrine resistant 0.69(0.46,1.05) 40/68(58.8) 55/70(78.6)
2L: PD post(neo)adj/metastatic Tx 0.46(0.20,1.05) 12/23(52.2) 17/23(73.9)
2L: PD post metastatic Tx only 0.67(0.40,1.11) 30/42(71.4) 38/45(84.4)
Prior Tamoxifen use
No 0.71(0.51,0.98) 69/110(62.7) 87/110(79.1)
Yes 0.55(0.35,0.88) 34/59(57.6) 42/62(67.7)
Estrogen receptor status
Positive 0.67(0.51,0.86) 102/167(61.1) 129/172(75.0)
Progesterone receptor status
Positive 0.67(0.49,0.91) 68/120(56.7) 99/132(75.0)
Negative 0.60(0.35,1.03) 33/46(71.7) 28/38(73.7)
Estr. & Progest. receptor status
Both positive 0.69(0.50,0.94) 67/118(56.8) 99/132(75.0)
Positive Negative 0.60(0.35,1.03) 33/46(71.7) 28/38(73.7)
Number of metastatic sites
< 3 0.59(0.43,0.83) 66/121(54.5) 81/113(71.7)
>= 3 0.77(0.50,1.20) 37/48(77.1) 48/59(81.4)
Visceral disease
No 0.69(0.45,1.06) 41/76(53.9) 45/72(62.5)
Yes 0.65(0.47,0.90) 62/93(66.7) 84/100(84.0)
0.0625 0.25 0.5 1 2 4
<---------- ---------->
Alpelisib better Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI

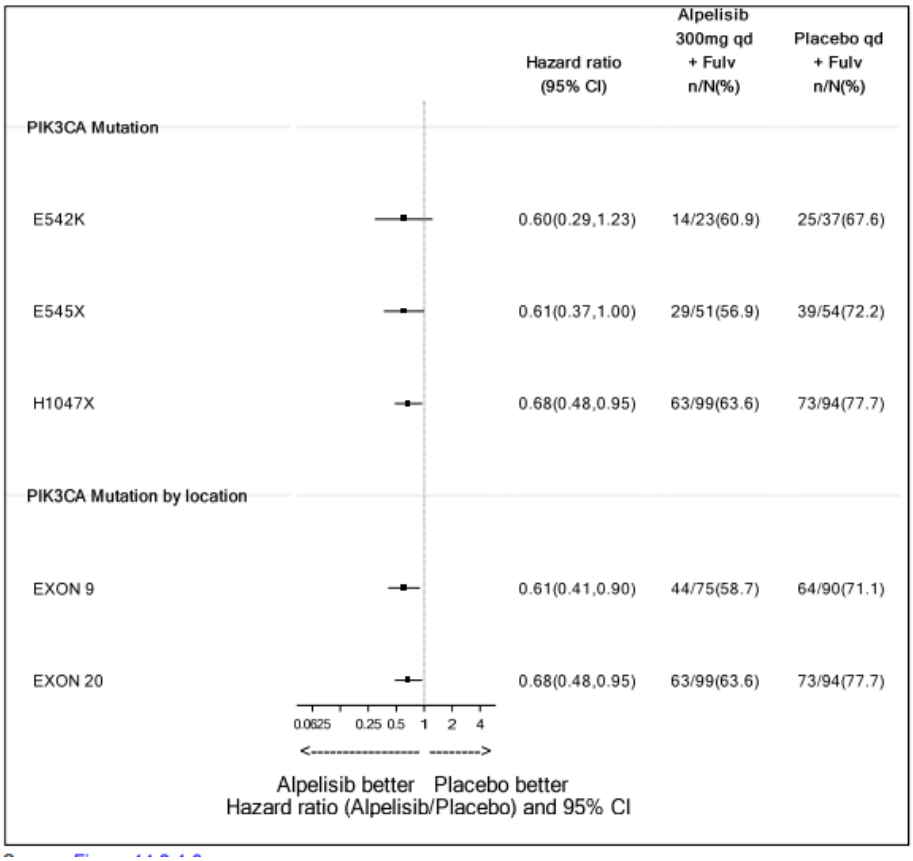


Figure 26: Forest plot for PFS per Investigator in different subgroups (FAS, PIK3CA mutant cohort)

PFS results for the subgroup of endocrine resistant patients (HR=0.64; 95% CI: 0.49, 0.85, n=292) and endocrine sensitive patients (HR=0.87; 95% CI: 0.35, 2.17, n=39) were in favour of the alpelisib plus fulvestrant arm.

Updated PFS analysis

Per protocol, no further statistical testing of PFS data after the primary PFS analysis was planned. However, descriptive analyses of PFS in the PIK3CA mutant and non-mutant cohorts have been performed with the new DCO of 30-Sep-2019.

Median duration of follow-up (from randomization date to the data cut-off date) among patients in the PIK3CA mutant cohort was 35.6 months, constituting approximately 15.6 months of additional follow-up since the cut-off date for the primary efficacy analysis (12-Jun-2018).

Compared with the primary efficacy analysis, a PFS event in the PIK3CA mutant cohort was reported for 20 additional patients in the alpelisib plus fulvestrant arm (123 vs 103 patients) and 19 additional patients in the placebo plus fulvestrant arm (148 vs 129).

Table 42: Analysis of PFS per local investigator assessment: primary efficacy analysis vs updated analyses (FAS, PIK3CA mutant cohort)

			Cox Model[1]	
	Events/N (%)	Median time (95% CI) (months)[2]	Hazard ratio[3]	95% CI
Primary analysis[4]				
Alpelisib 300mg qd + fulvestrant	103/169 (60.9)	11.0 (7.49,14.52)	0.65	(0.50,0.85)
Placebo qd + fulvestrant	129/172 (75.0)	5.7 (3.65,7.36)		
PFS update[5]				
Alpelisib 300mg qd + fulvestrant	110/169 (65.1)	11.0 (7.49, 14.52)	0.65	(0.50,0.84)
Placebo qd + fulvestrant	137/172 (79.7)	5.7 (3.65, 7.36)		
PFS update[6]				
Alpelisib 300mg qd + fulvestrant	123/169 (72.8)	11.0 (7.49, 14.52)	0.64	(0.50,0.81)
Placebo qd + fulvestrant	148/172 (86.0)	5.7 (3.65, 7.36)		

[1] Cox Proportional hazards model is stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases.

[2] Median PFS and its 95% CI are generated by KM estimation.

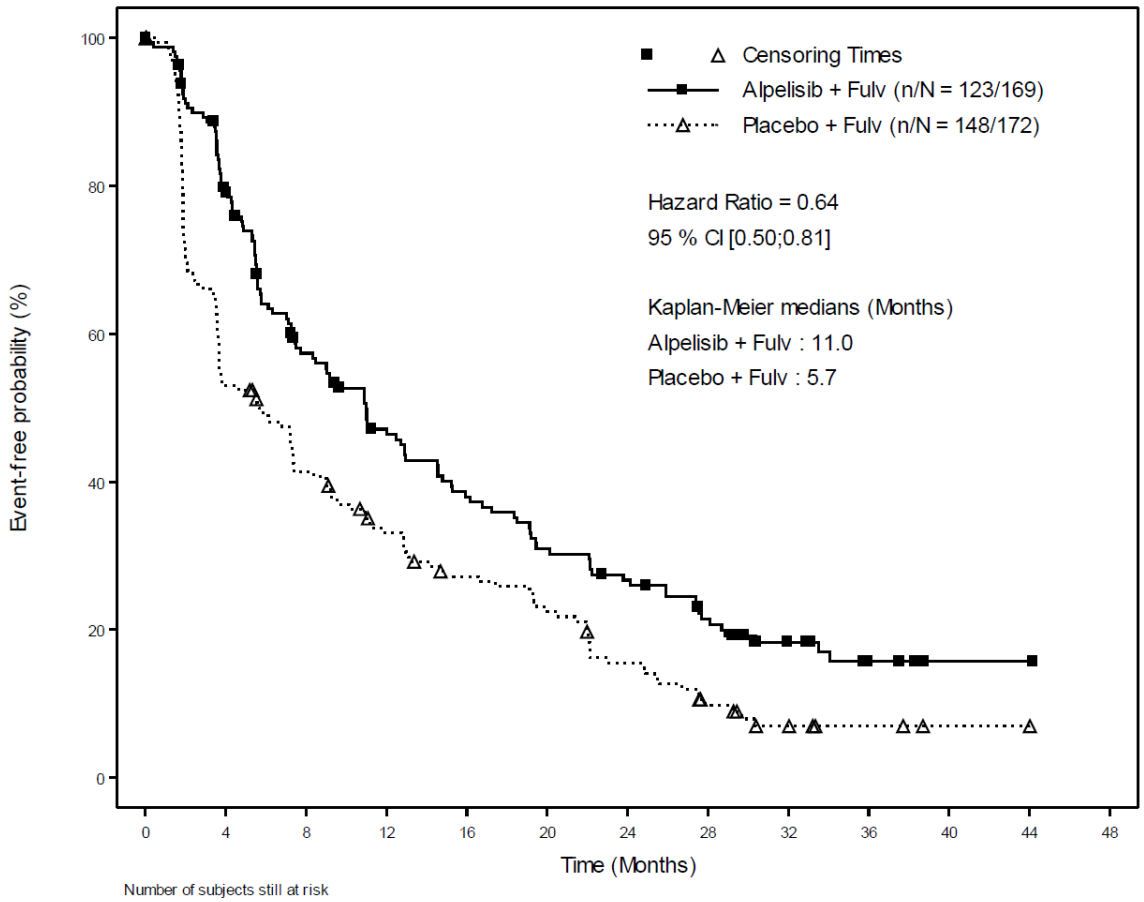
[3] Hazard Ratio for alpelisib + fulvestrant versus placebo + fulvestrant (placebo + fulvestrant is control).

[4] Data cut-off date: 12-Jun-2018

[5] Data cut-off date: 20-Oct-2018

[6] Data cut-off date: 30-Sep-2019

Source: [Study C2301-Table 11-1], [EU Day 120-Table 132-1], [Appendix 1-Table 14.2.1-1.1a]



Number of subjects still at risk

Time (Months)	0	4	8	12	16	20	24	28	32	36	40	44	48
Alpelisib + Fulv	169	123	85	66	54	44	37	28	18	8	1	1	0
Placebo + Fulv	172	89	67	51	40	33	22	12	6	3	1	1	0

Source: [Appendix 1-Table 14.2-1.1a]

Figure 27: Kaplan-Meier plot of progression-free survival as per local investigator assessment (FAS; PIK3CA mutant cohort) (DCO 12 June 2018)

Key secondary efficacy variable: OS in PIK3CA mutant cohort

As of the 12-Jun-2018 data cut-off date, OS data were immature with 92 of the 178 deaths reported corresponding to a 51.7% information fraction at the first interim OS analysis. The median OS was not yet reached for the alpelisib plus fulvestrant arm and was 26.9 months (95% CI: 21.9, NE) for the fulvestrant control arm. 69.2% of subjects in the alpelisib plus fulvestrant arm and 62.2% of subjects in the placebo plus fulvestrant arm were alive and were censored in this analysis.

Table 43: Analysis of OS (Full Analysis Set, PIK3CA mutant cohort) – Study C2301 (DCO 12 June 2018)

		Stratified log-rank test[1]		Stratified Cox model[1]	
	Events/N (%)	Median time (95% CI) (months)[2]	p-value[3]	Hazard ratio[4]	95% CI
Alpelisib arm	40/169 (23.7)	NE (28.12, NE)	0.06	0.73	(0.48, 1.10)
Placebo arm	52/172 (30.2)	26.9 (21.91, NE)			

[1] Both log-rank test and Cox PH model are stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases.
[2] Median (time to event) and its 95% CI are generated by KM estimation.
[3] P-value is one tailed and will be compared to pre-specified significance levels defined by the study.
[4] Hazard ratio of alpelisib plus fulvestrant vs. placebo plus fulvestrant (placebo plus fulvestrant is the control)
Source: [Study C2301-Table 14.2-2.11a]

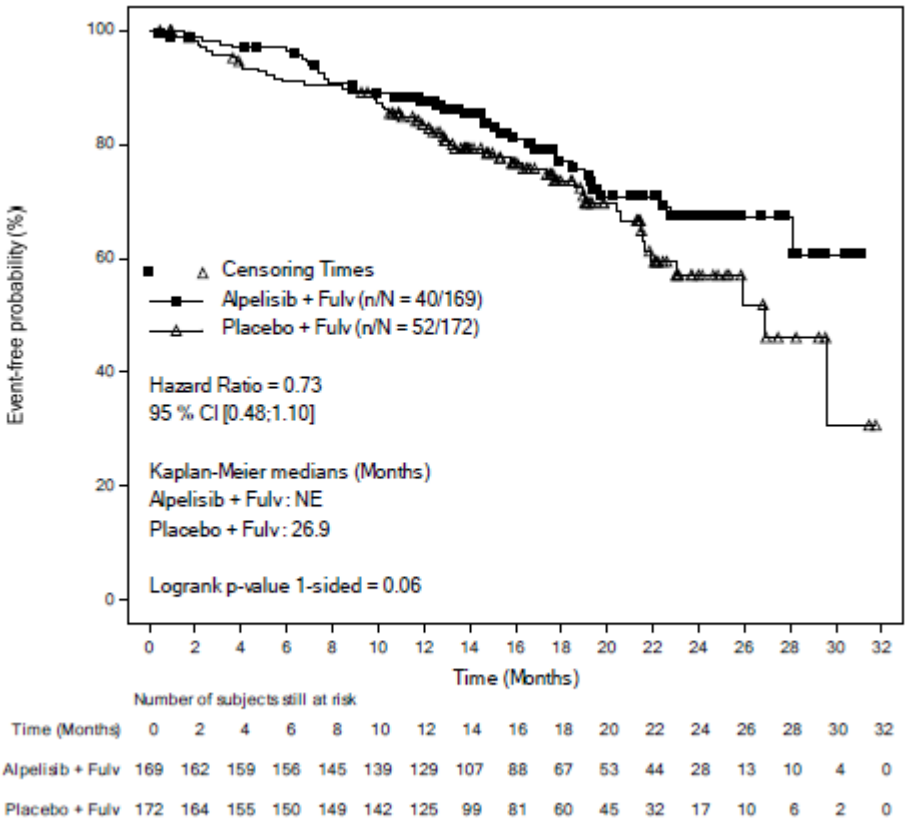


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Figure 28: Kaplan-Meier plot of OS (Full Analysis Set, PIK3CA mutant cohort) – Study C2301 (DCO 12 June 2018)

The second interim analysis of overall survival in the PIK3CA mutant cohort was conducted using a data cut-off date of 30-Sep-2019 and was based on 153 deaths corresponding to an 86.0% information fraction. The pre-specified O'Brien-Fleming stopping boundary (p-value ≤0.0117) was not crossed at this analysis. There were 69 events (40.8%) reported in the alpelisib plus fulvestrant arm, compared to 84 events (48.8%) in the placebo plus fulvestrant arm. A median OS difference of 9.4 months in favour of the patients receiving alpelisib plus fulvestrant was observed (40.6 months, 95% CI (32.2, NE) vs 31.2 months, 95% CI (26.8, NE)), which at the cut-off point for this interim analysis was not statistically significant at the required p-value of ≤0.0117 (HR=0.77, 95% CI: 0.56, 1.06, one-sided p-value = 0.06).

Secondary endpoint: PFS in patients with PIK3CA non-mutant tumours

PoC criteria for PFS per investigator assessment were not met in the non-mutant PIK3CA cohort. Median PFS was 7.4 months (95% CI: 5.4, 9.3) and 5.6 months (95% CI: 3.9, 9.1) respectively, in the alpelisib plus fulvestrant and placebo plus fulvestrant treatment arms, estimated HR = 0.85; 95% CI: 0.58; 1.25.

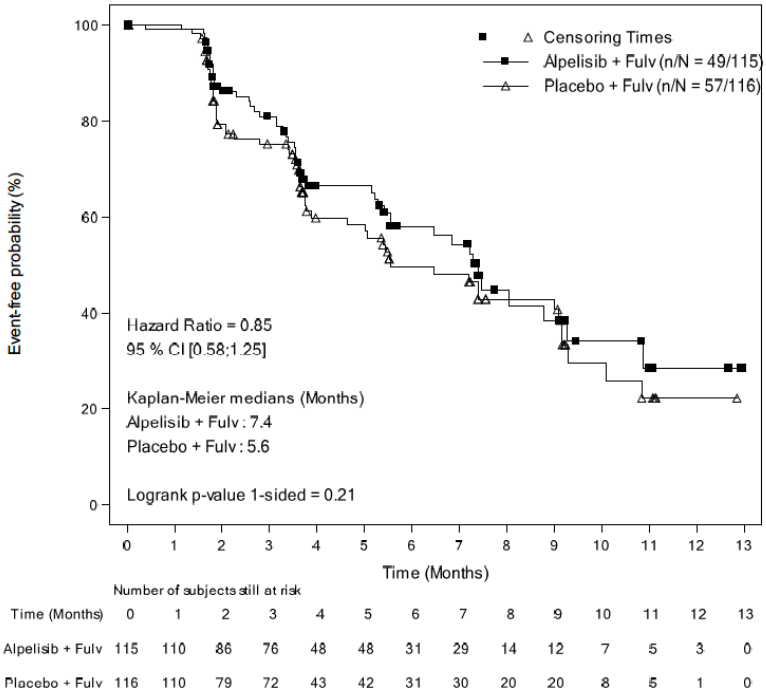
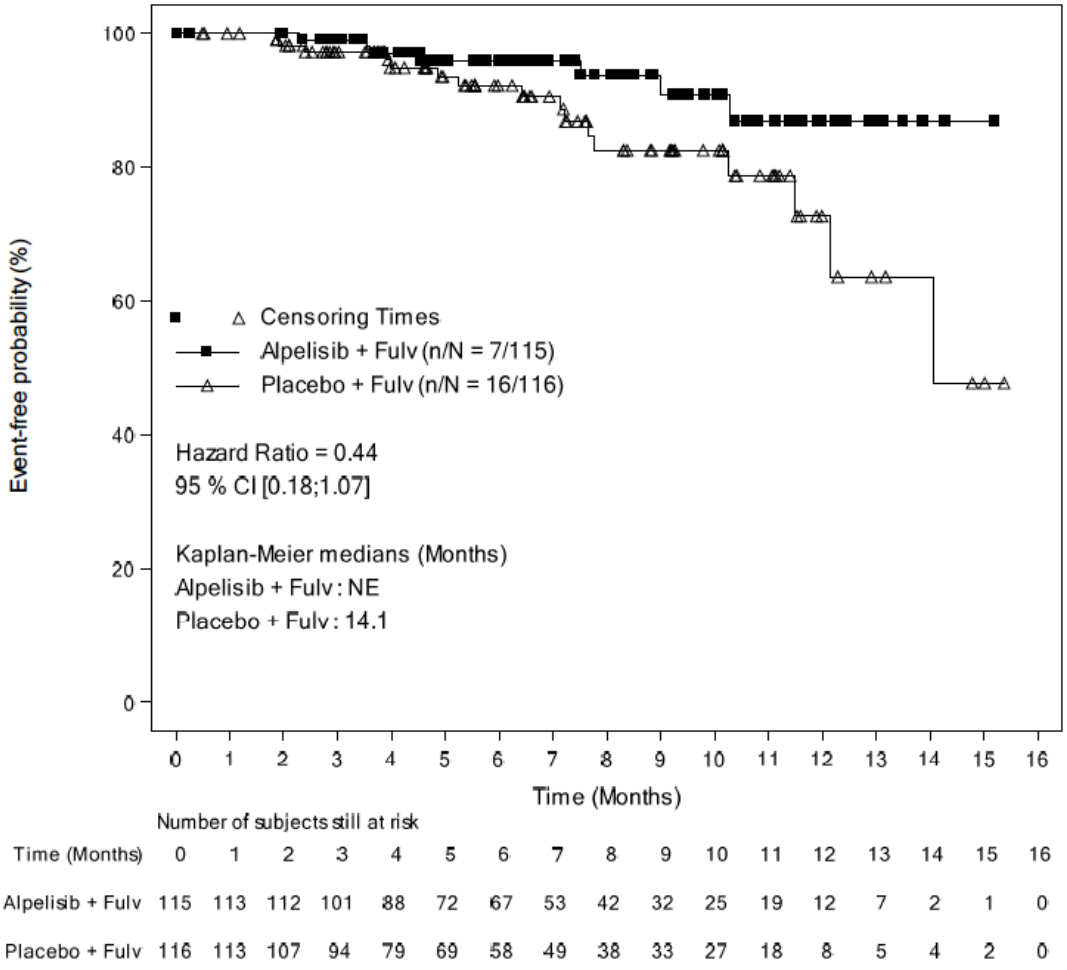


Figure 29: Kaplan-Meier plot of PFS per Investigator (FAS, PIK3CA non-mutant cohort) (DCO 23 Dec 2016)

Secondary endpoint: OS in subjects with PIK3CA non-mutant status

Statistical testing of OS was not applicable, since PFS did not meet the PoC criteria and was not statistically significant for this cohort. At the cut-off date of 23-Dec-2016, there were 23 deaths (18.4% of the total 125 planned for the final OS analysis): 7 (6.1%) in the alpelisib plus fulvestrant arm and 16 (13.8%) in placebo

plus fulvestrant arm. Median OS and the associated 95% CI were not estimable for the alpelisib plus fulvestrant arm and were 14.1 months (95% CI: 12.2, NE) for the placebo plus fulvestrant arm.



Number of subjects still at risk

Time (Months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Alpelisib + Fulv	115	113	112	101	88	72	67	53	42	32	25	19	12	7	2	1	0
Placebo + Fulv	116	113	107	94	79	69	58	49	38	33	27	18	8	5	4	2	0

Figure 30: Kaplan-Meier plot of overall survival (FAS, PIK3CA non-mutant cohort) (DCO 23 Dec 2016)

Table 44: Overall survival with different cut-off dates (FAS; PIK3CA non-mutant cohort)

			Cox Model[1]	
	Events/N (%)	Median time (95% CI) (months)[2]	Hazard ratio[3]	95% CI
OS analysis 23-Dec-2016[4]				
Alpelisib 300mg qd + fulvestrant	7/115 (6.1)	NE (NE, NE)	0.44	0.18, 1.07
Placebo qd + fulvestrant	16/116 (13.8)	14.1 (12.16, NE)		
Updated OS analysis[5]				
Alpelisib 300mg qd + fulvestrant	59/115 (51.3)	37.3 (27.89,45.37)	0.92	0.64, 1.33
Placebo qd + fulvestrant	59/116 (50.9)	34.3 (26.81,42.41)		

[1] Cox Proportional hazards model is stratified by Prior CDK4/6 inhibitor usage and presence of lung/liver metastases.
[2] Median OS and its 95% CI are generated by KM estimation.
[3] Hazard Ratio for alpelisib + fulvestrant versus placebo + fulvestrant (placebo + fulvestrant is control).
[4] Data cut-off date: 23-Dec-2016
[5] Data cut-off date: 30-Sep-2019
Source: [Study C2301-Table 14.2-2.11b], [Appendix 1-Table 14.2-2.11b]

Secondary endpoint: Overall response rate and time to response

In the full analysis subset, ORR was 26% vs. 11.6%, and progressive disease was 9.5% vs. 30.8% in the alpelisib plus fulvestrant arm relative to the placebo plus fulvestrant arm in the PIK3CA mutant cohort.

Table 45: Best overall response summary table per Investigator assessment in PIK3CA mutant and PIK3CA non-mutant cohorts (FAS) (DCO 12 June 2018 and DCO 23 December 2016 respectively)

	PIK3CA mutant cohort					PIK3CA non-mutant cohort				
	Alpelisib + fulvestrant N=169		Placebo + fulvestrant N=172		P value	Alpelisib + fulvestrant N=115		Placebo + fulvestrant N=116		P value
	n (%)	95% CI	n (%)	95% CI		n (%)	95% CI	n (%)	95% CI	
Subjects with measurable disease at Baseline	126 (74.6)		136 (79.1)			91 (79.1)		94 (81.0)		
Subjects with non-measurable disease only at Baseline	43 (25.4)		36 (20.9)			24 (20.9)		22 (19.0)		
Best overall response										
Complete response (CR)	1 (0.6)	(0.0, 3.3)	2 (1.2)	(0.1, 4.1)		1 (0.9)	(0.0, 4.7)	0	(NA, NA)	
Partial response (PR)	44 (26.0)		20 (11.6)			14 (12.2)		12 (10.3)		
Stable disease (SD)	58 (34.3)		63 (36.6)			57 (49.6)		52 (44.8)		
Progressive disease (PD)	16 (9.5)		53 (30.8)			19 (16.5)		26 (22.4)		
Non-CR/Non-PD (NCRNPD)	38 (22.5)		25 (14.5)			19 (16.5)		19 (16.4)		
Unknown (UNK)	12 (7.1)		9 (5.2)			5 (4.3)		7 (6.0)		
Overall response rate (ORR: CR+PR)	45 (26.6)	(20.1, 34.0)	22 (12.8)	(8.2, 18.7)	0.0006	15 (13.0)	(7.5, 20.6)	12 (10.3)	(5.5, 17.4)	0.27
Clinical benefit rate (CR+PR+SD+Non-CR/Non-PD ≥ 24 weeks)	104 (61.5)	(53.8, 68.9)	78 (45.3)	(37.8, 53.1)	0.002	45 (39.1)	(30.2, 48.7)	36 (31.0)	(22.8, 40.3)	0.10

In the PIK3CA mutant cohort, using a data cut-off date of 12-Jun-2018, the overall response rate in patients with measurable disease at baseline was 35.7% (95% CI: 27.4, 44.7) in the alpelisib plus fulvestrant arm and 16.2% (95% CI: 10.4, 23.5) in the placebo plus fulvestrant arm.

Ancillary analyses

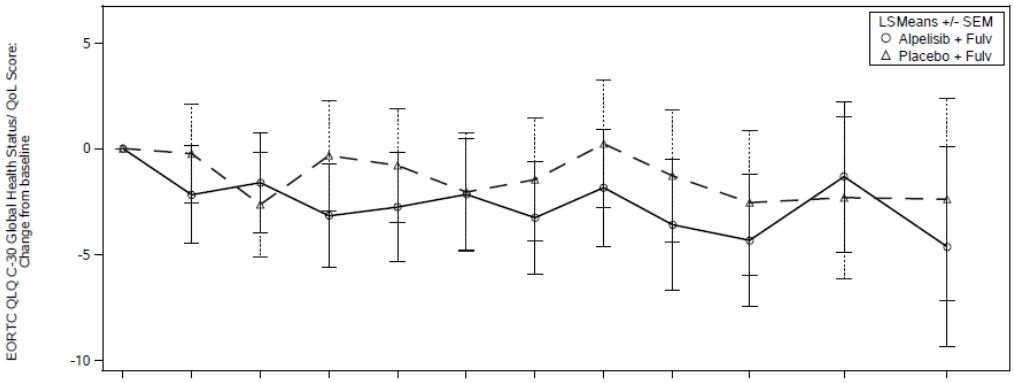
Exploratory endpoint: time to response and duration of response (DCO 12 Jun 2018)

In PIK3CA mutant cohort, treatment with alpelisib in combination with fulvestrant was associated with numerical trends in favour of a shorter time to response compared with fulvestrant alone. The estimated probability of achieving a response by 6 months was 26.0% (95% CI: 19.86, 33.60) in the alpelisib plus fulvestrant arm (n=45) and 9.5% (95% CI: 5.95, 15.07) in the placebo plus fulvestrant arm (n=23).

Among subjects with a response (CR or PR), median duration of response was 12.6 months (95% CI: 8.5, 18.5) in the alpelisib plus fulvestrant arm (n=25) and 14.8 months (95% CI: 10.12, NE) in the placebo plus fulvestrant arm (n=9).

Secondary endpoint: change from baseline in global health status (DCO 12 Jun 2018)

The median times to 10% deterioration in global health status/QoL scare score of EORTC QLC-C30 were 14.8 vs 14.8 months in the alpelisib plus fulvestrant and placebo plus fulvestrant arms, respectively (HR=1.03; 95% CI: 0.72, 1.48).



Alpelisib + Fulv	155	137	120	100	81	70	65	54	35	34	22	10
Placebo + Fulv	159	133	103	80	70	60	49	41	36	26	18	10

- The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as derived from the repeated measurement model.
- The mixed effect model includes terms for treatment, stratification factors, baseline value, time and time * treatment interaction.
This analysis only includes assessments up to the time point where there are at least 10 patients on each of the treatment groups

Figure 31: Summary of change from baseline in EORTC QLQ-C30 global health status/QOL scale score (Full Analysis Set, PIK3CA mutant cohort) – Study C2301

Table 46: Overall summary of time to 10% deterioration in EORTC QLQ-C30 global health status/QoL scale score (Full Analysis Set, PIK3CA mutant cohort) – Study C2301 (DCO 12 Jun 2018)

	Alpelisib plus fulvestrant arm N=169	Placebo plus fulvestrant arm N=172
n/N (%)	66/169 (39.1)	58/172 (33.7)
Maximum follow-up	33.31	32.39
Median follow-up	20.17	19.94
Percentiles (95% CI) [1]:		
25th	5.55 (3.61, 7.33)	3.75 (3.55, 9.20)
50th	14.75 (9.66, NE)	14.78 (11.50,19.45)
75th	26.32 (26.32, NE)	24.84 (19.45, NE)
% event-free probability estimates (95% CI) [2]:		
6 months	70.05 (61.52,77.04)	70.98 (61.93,78.25)
12 months	56.27 (46.79,64.71)	59.75 (49.43,68.63)
18 months	39.95 (29.01,50.64)	43.02 (31.09,54.38)

[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point. Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of KM estimates.
n: Total number of events included in the analysis.
N: Total number of subjects included in the analysis.
Source: [Study C2301-Table 14.2-2.56a]

Secondary endpoint: time to definitive deterioration of ECOG PS (DCO 12 Jun 2018)

In PIK3CA mutant cohort, sixty-seven percent of subjects had an ECOG performance status score of 0 at baseline and 33.3% of subjects an ECOG performance status score of 1 in the alpelisib plus fulvestrant arm compared to 66.1% of subjects with an ECOG performance status score of 0 and 33.9% with a score of 1 at baseline in the placebo plus fulvestrant arm. No differences were observed between treatment arms in the time to definitive deterioration (TDD) of ECOG performance status (HR = 1.00; 95% CI: 0.65, 1.53).

There were 44 subjects (26.0%) in the alpelisib arm and 41 subjects (23.8%) in the placebo arm who met the definitive deterioration criteria. The median TDD in ECOG performance status was 26.3 months (95% CI: 26.3, NE) in the alpelisib arm and was not reached (95% CI: 20.4, NE) in placebo arm.

The estimated Kaplan-Meier probability of no definitive deterioration in ECOG performance status at 12 months was similar between the two treatment arms: 73.2% (95% CI: 64.7, 79.9) in the alpelisib arm vs. 70.2% (95% CI: 60.6, 77.9) in the placebo arm.

Exploratory endpoint: PFS2

Table 47: PFS2 per local investigator assessment with different cut-off dates, by cohort (FAS)

Cohort Cut-off date	Alpelisib + fulvestrant Events/N (%)	Alpelisib + fulvestrant Median time (95% CI) (months)[2]	Placebo + fulvestrant Events/N (%)	Placebo + fulvestrant Median time (95% CI) (months)[2]	HR (95% CI)[1]
PIK3CA mutant					
12-Jun-2018	70/169 (41.4)	22.8 (19.0, 28.1)	84/172 (48.8)	18.5 (13.9, 23.6)	0.73 (0.53, 1.01)
20-Oct-2018	80/169 (47.3)	22.6 (19.0, 28.1)	91/172 (52.9)	18.9 (14.1, 25.9)	0.77 (0.57, 1.05)
30-Sep-2019	106/169 (62.7)	22.8 (18.5, 26.3)	119/172 (69.2)	18.2 (12.8, 22.2)	0.78 (0.60, 1.02)
PIK3CA non-mutant					
23-Dec-2016	21/115 (18.3)	14.9 (12.2, 14.9)	24/116 (20.7)	13.0 (10.9, 14.1)	0.82 (0.45, 1.49)
20-Oct-2018	74/115 (64.3)	19.3 (12.9, 22.4)	74/116 (63.8)	15.7 (13.3, 20.7)	0.92 (0.66, 1.27)
30-Sep-2019	87/115 (75.7)	19.3 (12.9, 21.9)	87/116 (75.0)	15.7 (13.3, 20.7)	0.92 (0.68, 1.24)

[1] Hazard ratios from Cox PH model stratified by Prior CDK4/6 inhibitor usage and presence of lung/liver metastases, presented for the alpelisib plus fulvestrant arm compared to the placebo plus fulvestrant arm; placebo is the control.

[2] Median PFS2 and its 95% CI are generated by KM estimation.

Source: [Study C2301-Table 14.2-4.1a], [Study C2301-Table 14.2-4.1b], [EU D120-Table 145-1a], [EU D120-Table 145-1b], [Appendix 1-Table 14.2-4.1a], [Appendix 1-Table 14.2-4.1b]

Biomarkers

PIK3CA mutations in tumour samples

PIK3CA mutation status at baseline was determined using archival tumour tissue samples or available samples from most recent tumour tissue biopsy ("fresh"). Samples were predominantly archival (92%, 525 of the 572 randomized subjects. Of the 572 randomized subjects, 341 subjects had detectable PIK3CA mutations as determined by real-time PCR assays. Of these 341 with PIK3CA mutations, primary breast tumour biopsies were used for 262 subjects, metastatic tumour biopsies were used for 74 subjects, and tumour type was unknown for five subjects. Of the 231 subjects with no detectable PIK3CA mutations, primary tumour biopsies were used for 174 subjects, metastatic tumour biopsies were used for 51 subjects, and tumour type was unknown for six subjects. Of the 572 randomized subjects, the frequencies of mutations in the C2 domain (exon 7), helical domain (exon 9), and kinase domain (exon 20) were 1.0%, 28.8%, and 33.7% respectively. The frequencies of exon 7, 9, and 20 mutations were similar across treatment arms and biopsy types. Within the helical domain, the most frequent mutations were E542K and E545K/X and within the kinase domain the most frequent mutations were H1047R/X. E545X denotes mutations inclusive of E545A/D/G/K and H1047X denotes mutations inclusive of H1047L/R/Y.

PIK3CA mutation by ctDNA

PIK3CA mutation status using real-time PCR was determined using plasma ctDNA samples collected from randomized subjects at baseline on Cycle 1 Day 1 prior to initiation of therapy. Of the 572 randomized subjects, 186 had a detectable PIK3CA mutation by ctDNA and 363 subjects had no detectable PIK3CA

mutations by ctDNA. ctDNA results were missing for 23 subjects due to no sample being collected or the sample was collected after initiation of therapy. PIK3CA mutation status by ctDNA was well balanced across treatment arms. Of the 572 randomized subjects, the frequencies of mutations in the C2 domain (exon 7), helical domain (exon 9) and kinase domain (exon 20) based on ctDNA were 0.3%, 12.8%, and 19.6%, respectively. Within the helical domain, the most frequent mutations by ctDNA were E542K and E545K. Within the kinase domain, the most frequent mutation was H1047R. Of the 341 subjects with PIK3CA mutations by tissue, 322 had PIK3CA results by ctDNA of whom 178 (55.3%) had a PIK3CA mutation by ctDNA. Of the 231 subjects with no detectable PIK3CA mutation by tissue, 227 had PIK3CA results by ctDNA of whom 219 (96.5%) had no detectable PIK3CA mutations by ctDNA. The percentage of subjects with agreement between ctDNA and tissue was similar for both tissue sample types (primary and metastatic).

Table 48: Summary of concordance between mutational status from tissue biopsy versus circulating tumour DNA - All tumours Full Analysis Set

All subjects (N=572)

	Circulating tumor DNA			
Tissue	Non-Mutant n(%)	Mutant n(%)	Missing n(%)	
Non-Mutant n(%)	219 (38.3)	8 (1.4)	4 (0.7)	231
Mutant n(%)	144 (25.2)	178 (31.1)	19 (3.3)	341
	363	186	23	572

Summary of main efficacy results

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

Table 49: Summary of efficacy for trial C2301

Title: A Phase III randomized double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment		
Study identifier	CBYL719C2301 - EudraCT no. 2015-000340-42	
Design	Randomized, double-blind, placebo-controlled, international multicentre Phase III study to evaluate the efficacy and safety of treatment with alpelisib plus fulvestrant vs. placebo plus fulvestrant in men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer which progressed on or after AI treatment.	
	Duration of main phase: Duration of Run-in phase:	Until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. 35 days

Hypothesis	Superiority		
Treatments groups Randomization 1:1 in both cohort (PIK3CA mutant	Alpelisib 300 mg orally q.d + fulvestrant 500 mg (im) on D1 and 15 of C1 and D1±3 of a 28 day cycle thereafter		PIK3CA mutant cohort: 169 PIK3CA non-mutant cohort: 115
	Placebo daily + fulvestrant 500 mg (im) on D1 and 15 of C1 and D1±3 of a 28 day cycle thereafter		PIK3CA mutant cohort: 172 PIK3CA non-mutant cohort: 116
Endpoints and definitions	Primary endpoint	PFS in the PIK3CA mutant cohort	Death (any cause)+PD FAS population – Local radiology assessment (RECIST1.1)
	Secondary endpoint	OS in the PIK3CA mutant cohort	Death (any cause) FAS population
		PFS in the PIK3CA non-mutant cohort (PoC)	Death (any cause)+PD FAS population – Local radiology assessment (RECIST1.1)
		OS in the PIK3CA non-mutant cohort (PoC)	Death (any cause) FAS population
		ORR in the PIK3CA mutant cohort	CR+PR FAS population – Local radiology assessment (RECIST1.1)
		ORR in the PIK3CA non-mutant cohort	CR+PR FAS population – Local radiology assessment (RECIST1.1)
Database lock	12-Jun-2018 (PIK3CA mutant cohort) – 23-Dec-2016 (PIK3CA non-mutant cohort)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point	Full analysis set (FAS): all subjects who were randomized to study treatment Final PFS analysis Interim OS			
Descriptive statistics and estimate variability		PIK3CA mutant cohort		PIK3CA non-mutant cohort
		Alpelisib + fulvestrant	Placebo + fulvestrant	Alpelisib + fulvestrant	Placebo + fulvestrant
	Number of subjects	169	172	115	116
	PFS Event (%) Median time (months) [a] (95% CI)	103 11.0 (7.49,14.52)	129 5.7 (3.65,7.36)	49 7.4 (5.42, 9.26)	57 5.6 (3.88, 9.10)
	OS Event (%) Median time (months) [a] (95% CI)	40 NE (28.12, NE)	52 26.9 (21.91,NE)	7 (6.1) NE (NE,NE)	16 (13.8) 14.1 (12.16,NE)

	ORR[b] n (%) 95% CI	45 (26.6) (20.1,34.0)	22(12.8) (8.2, 18.7)	15 (13.0) (7.5, 20.6)	12 (10.3) (5.5, 17.4)

Effect estimate per comparison	Primary endpoint: PFS in PIK3CA	Comparison groups	Alpelisib+fulvestrant vs Placebo+fulvestrant
		Hazard ratio[c]	0.65
		(95% CI) [c]	(0.50,0.85)
		P-value(stratified log-rank)[d]	0.00065
	Secondary endpoint: OS in PIK3CA mutant cohort	Comparison groups	Alpelisib+fulvestrant vs Placebo+fulvestrant
		Hazard ratio[c]	0.73
		(95% CI) [c]	(0.48,1.10)
		P-value(stratified log-rank)[d]	0.06
	Secondary endpoint: PFS in PIK3CA non-mutant cohort (PoC)	Comparison groups	Alpelisib+fulvestrant vs Placebo+fulvestrant
		Hazard ratio[c]	0.85
		(95% CI) [c]	(0.58,1.25)
		P-value(stratified log-rank)[d]	0.21
	Secondary endpoint: OS in PIK3CA non-mutant cohort (PoC)	Comparison groups	Alpelisib+fulvestrant vs Placebo+fulvestrant
		Hazard ratio [c]	0.44
		(95% CI) [c]	(0.18,1.07)
		P-value(stratified log-rank)[d]	[e]
	Secondary endpoint: ORR in PIK3CA mutant cohort	Comparison groups	Alpelisib+fulvestrant vs Placebo+fulvestrant
		P-value(Cochran-Mantel Haenszel)	0.0006
	Secondary endpoint: ORR in PIK3CA non-mutant cohort	Comparison groups	Alpelisib+fulvestrant vs Placebo+fulvestrant
		P-value(Cochran-Mantel Haenszel)	0.27
Notes	[a] Generated by KM estimation [b] subjects with measurable and non-measurable disease at Baseline [c] Stratified Cox model [d] one-sided p-value [e] p-value was not calculated because PFS in non-mutant cohort did not met the PoC criteria and was not statistically significant.		

Analysis performed across trials (pooled analyses and meta-analysis)

The efficacy claim for subjects with a PIK3CA mutation is based primarily on data from Phase III Study C2301. Supportive data are provided from the combination dose-expansion part of the Phase IA Study X2101. No comparisons were provided between the respective efficacy results from these studies nor were the data pooled given the differences in indication, dose and schedule, and treatment regimen.

Clinical studies in special populations

No special subject populations were evaluated. As the eligibility criteria required subjects to have adequate renal and hepatic function, specific subgroup analyses of subjects with renal or hepatic impairment in the targeted subject population were not feasible.

The table below summarises patients in special populations, i.e. grouped by age treated in the main clinical studies CBYL719C2301 (controlled), CBYL719X1101 and CBYL719X2101 (both uncontrolled).

Table 50: Clinical studies in special populations (Full Analysis Set)

	Age 65-74 n/N (%)	Age 75-84 n/N (%)	Age 85+ n/N (%)
Controlled Trials			
CBYL719C2301	178/572 (31.1)	68/572 (11.9)	5/572 (0.9)
Non Controlled Trials			
CBYL719X1101	6/33 (18.2)	1/33 (3.0)	-
CBYL719X2101			
Single agent administration	28/134 (20.9)	11/134 (8.2)	-
Combination administration	16/87 (18.4)	2/87 (2.3)	-
Source: [Table 147-1], [Table 147-2], [Table 147-3], [Table 147-4]			

Supportive studies

Study X2101

Study X2101 is a multicenter, Phase IA, dose-escalation/expansion study of oral alpelisib in adult subjects with advanced solid malignancies.

Table 51: Summary of Phase IA combination expansion part – Study X2101

Study objective and population	Combination expansion: To assess the overall safety and tolerability of alpelisib treatment in combination with fulvestrant in subjects with ER-positive, HER2-negative breast cancer whose tumors had an alteration of the PIK3CA gene and in subjects with PIK3CA wild- type breast cancer.
Efficacy endpoints	Efficacy endpoints were secondary endpoints in this study. These included: BOR, ORR, DCR, CBR, and PFS.
No of subjects	87 subjects were enrolled in the alpelisib plus fulvestrant combination treatment group (all dose groups): 28 in the dose-escalation part and 59 in the dose-expansion part. 52 subjects had centrally confirmed alteration of the PIK3CA gene (mutation or amplification), 33 subjects had centrally confirmed PIK3CA wild-type and 2 subjects with unknown status for PIK3CA gene by central laboratory analysis. During the dose escalation, 9 subjects were randomized to the alpelisib 300 mg plus fulvestrant arm (all PIK3CA altered) (corresponding to the dosage regimen that was used in Study C2301 and for which approval is being sought).
Regimen	Alpelisib was administered orally daily, on a continuous schedule together with fulvestrant (500 mg intramuscularly [as two 5-mL injections] on Days 1 and 15 of Cycle 1 and on Day 1 ± 3 days of every 28-day cycle thereafter)
Treatment duration	Alpelisib was taken up to disease progression or unacceptable toxicity that precluded any further treatment and/or treatment was discontinued at the discretion of the investigator or by subject refusal.
Tumor assessment	Tumor assessments were performed using RECIST 1.0 for all subjects. All potential sites of tumor lesions were assessed at screening/baseline by radiologic techniques using thoracic, abdominal, and pelvic CT or MRI (although CT was the preferred imaging modality), complemented with brain scans in case of clinical evidence of metastatic brain disease. In addition, a bone scan was also performed for subjects with clinical evidence of bone metastases. Subsequent scans were performed at the end of Cycle 2, and every 8 weeks thereafter (i.e. at the end of Cycles 4, 6, 8, etc.), and at study treatment completion. All assessments were performed within 7 days prior to the scheduled day of assessment. The assessment at the end of study treatment visit was only performed if the prior assessment occurred ≥ 21 days before.
Statistical methodology	BOR, ORR, DCR, and CBR were summarized as percentages with exact binomial two-sided 95% CIs. BOR was also displayed using waterfall plots. PFS: the survival distribution of PFS was estimated using the Kaplan-Meier method. The PFS hazard ratio with the two-sided 95% CI were derived from the Cox proportional hazards model. Kaplan-Meier estimates with 95% CIs were also summarized at specific time points (2, 4, and 6 months)

BOR: best overall response, CBR: clinical benefit rate, DCR: disease control rate, ORR: overall response rate, PFS: progression-free survival

87 postmenopausal women with ER-positive locally advanced or metastatic breast cancer who had disease progression during or following anti-estrogen therapy or whose disease had relapsed following adjuvant anti-estrogen therapy were treated with alpelisib and fulvestrant.

Alpelisib was dosed at 300 mg (n = 9), 350 mg (n = 8), and at the MTD of 400 mg (n = 70). All 87 subjects were heavily pretreated, with a median of 5.0 prior antineoplastic regimens, 86 had undergone prior surgery, 66 subjects received prior chemotherapy and 65 received prior radiotherapy. Prior anti-estrogen therapy was received by 53 subjects in the metastatic setting.

Among the 87 subjects, 52 subjects harboured an alteration of the PIK3CA gene (mutation or amplification) and 33 subjects had PIK3CA wild-type.

Of the 49 evaluable subjects with ER-positive, HER2-negative breast cancer with PIK3CA mutation, the ORR was 28.6% (95% CI: 16.6, 43.3).

The PFS analysis demonstrated that the alpelisib plus fulvestrant combination was associated with prolonged PFS among the 49 subjects with PIK3CA mutant tumours (median PFS: 9.1 months (95% CI: 7, 15)) relative to the 32 evaluable subjects with PIK3CA wild-type tumours (where the median PFS was 4.7 months (95% CI: 2, 6)).

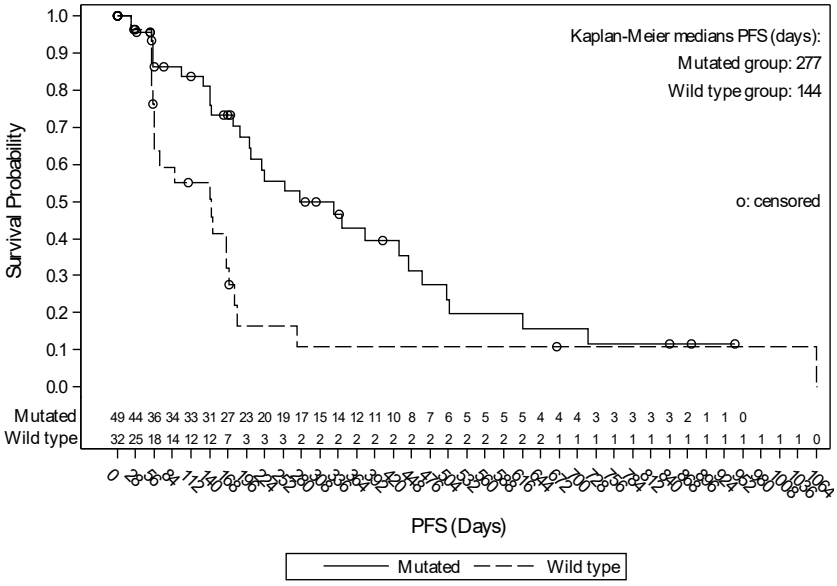


Figure 32: Kaplan-Meier plot of PFS per investigator assessment in ER-positive, HER2-negative subjects with advanced breast cancer by PIK3CA alteration status - combination agent (Full Analysis Set) – Study X2101

Overall, 39 subjects reported prior fulvestrant use and were subsequently exposed to alpelisib plus fulvestrant with alpelisib doses of 300 mg, 350 mg, or 400 mg. The duration of fulvestrant was up to 180 days (approx. 6 months) in 18 of the 39 subjects. Of the 39 subjects, 21 had measurable disease at baseline and PIK3CA mutations. The best overall responses to treatment with alpelisib plus fulvestrant for these 21 subjects were partial response in 7 subjects, stable disease in 11 subjects, and progressive disease in 2 subjects. For 1 subject, the best overall response is unknown.

Study BYLieve (Study CBYL719X2402)

This is a Phase II, multicentre, open-label, three-cohort, non-comparative study. This trial was designed to evaluate the use of alpelisib in combination with endocrine therapy (either fulvestrant or letrozole) in patients with HR-positive, HER2-negative advanced breast cancer whose tumour harboured a PIK3CA mutation and whose disease had progressed on or after prior treatment, including CDK 4/6 inhibitor-based therapy.

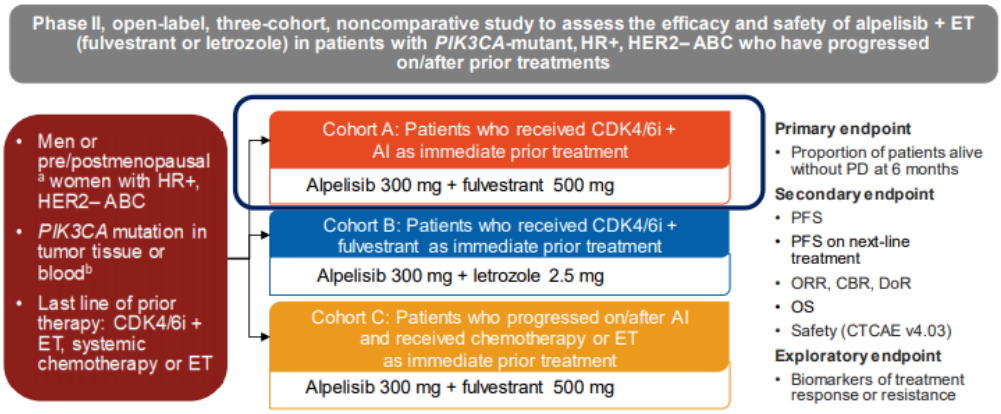


Figure 33: Study design - BYLieve

A total of 127 patients were enrolled to Cohort A. The primary analysis was performed for the modified Full analysis set (mFAS), defined as all subjects in Cohort A with a PI3KCA mutation confirmed by a Novartis-designated laboratory (n = 121). The median duration of follow-up (from enrollment to the DCO date) was 11.7 months. The median duration of exposure to alpelisib was 5.1 months, and for fulvestrant was 6.5 months.

Table 52: Demographic and baseline characteristics: BYLieve Cohort A

Demographic variable	Alpelisib plus fulvestrant – Cohort A (prior CDK4/6i use and confirmed PIK3CA mutation) N = 121
Median age (years)	57.0
Minimum, maximum	33, 83
Age category, n (%)	
< 50 years	35 (28.9)
≥ 50 to < 65 years	55 (45.5)
≥ 65 years	31 (25.6)
Race, n (%)	
Caucasian	77 (63.6)
Asian	12 (9.9)
Black	5 (4.1)
Other	2 (1.7)
Unknown/missing	23 (19.0)
ECOG performance status, n (%)	
0	78 (64.5)
1	38 (31.4)
2	2 (1.7)
Missing	3 (2.5)

Table 53: Disease history: BYLieve Cohort A

Disease history	Alpelisib plus fulvestrant – Cohort A (prior CDK4/6i use and confirmed PIK3CA mutation) N = 121
Time since initial diagnosis	
Median	56.6
Minimum, maximum	6.2-408.7
Time since most recent recurrence/relapse (mo)	
Median	1.6
Minimum, maximum	0.1, 16.1
Stage at study entry, n (%)	
III	3 (2.5)
IV	118 (97.5)
Types of lesion at baseline, n (%)	
Both target and non-target	118 (97.5)
Target only	2 (1.7)
Non-target only	1 (0.8)
Current extent of disease (metastatic sites), n (%)	
Bone	103 (85.1)
Bone only	22 (18.2)
Visceral	82 (67.8)
Lung	56 (46.3)
Liver	43 (35.5)
Other visceral	8 (6.6)
Lymph nodes	35 (28.9)
Breast	5 (4.1)
Skin	4 (3.3)
Other	10 (8.3)
Number of lines of prior medication therapy in metastatic setting, n (%)	
0	14 (11.6)
1	85 (70.2)
2	21 (17.4)
3	1 (0.8)

The primary endpoint was defined as the proportion of subjects who are alive without disease progression at 6 months based on local investigator assessment using RECIST v1.1. A proportion of 30% of patients was considered to be a clinically meaningful threshold for all cohorts in this study, and therefore the primary objective for each cohort was met if the lower bound of the two-sided exact 95% CI of the proportion of non-progressors was > 30%. Patients who progressed, died, or discontinued from the study before 6 months were counted as 'failures' in the analysis. In Cohort A, the proportion of subjects who were alive without disease progression at 6 months was 50.4% (95% CI: 41.2, 59.6), with the lower bound of the 95% CI exceeding 30%.

Table 54: Efficacy results: BYLieve Cohort A (N=151) (investigator-reported response)

Proportion of patients who are alive without disease progression at 6 months (%), (95% CI)	61	50.4 (41.2, 59.6)
Median PFS (mo), (95% CI)	72	7.3 (5.6, 8.3)
ORR (%), (95% CI)	21	17.4 (11.1, 25.3)
Decrease in best % change from baseline (%)	87	70.1
Median DoR (mo), (95% CI)	9	6.6 (4.3, NE)

Table 55: Best overall response as per local investigator assessment (modified Full analysis set)

	Cohort A N=121		Cohort B N=73	
	n (%)	95% CI	n (%)	95% CI
Subjects with measurable disease at Baseline	100(82.6)		67(91.8)	
Subjects with non-measurable disease only at Baseline	19(15.7)		6(8.2)	
Best overall response				
Complete response (CR)	0		0	
Partial response (PR)	21(17.4)		13(17.8)	
Non-CR/Non-PD (NCRNPD)	16(13.2)		4(5.5)	
Stable disease (SD)	55(45.5)		34(46.6)	
Progressive disease (PD)	14(11.6)		15(20.5)	
Unknown (UNK)	15(12.4)		7(9.6)	
<Not Assessed>	0		0	
Overall response rate (ORR: CR+PR)	21(17.4)	(11.1,25.3)	13(17.8)	(9.8,28.5)
Clinical benefit rate (CBR: CR+PR +(SD+Non-CR/Non-PD>=24 weeks))	55(45.5)	(36.4,54.8)	20(27.4)	(17.6,39.1)

Cohort A: Alpelisib + fulvestrant; Cohort B: Alpelisib + letrozole.
N: The total number of subjects in the Cohort. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The 95% CI for the frequency distribution of each variable were computed using Clopper and Person (1934).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy data supporting this marketing authorisation application rely on the pivotal Study C2301 (SOLAR-1), a randomised, double-blind, placebo-controlled, international, multicentre Phase III study comparing alpelisib plus fulvestrant vs. placebo plus fulvestrant in postmenopausal women and men with HR-positive, HER2-negative ABC after aromatase inhibitor failure, harbouring PIK3CA mutations. Supportive evidence from 49 patients treated in a dose-escalation phase 1 study X2101 was also considered. Furthermore, supportive data were presented from study BYLieve, a phase II, multicentre, open-label, three-cohort, non-comparative study designed to evaluate the use of alpelisib in combination with endocrine therapy in patients with HR-positive, HER2-negative, advanced breast cancer with a PIK3CA mutation whose disease had progressed on or after prior treatment, including CDK 4/6 inhibitor-based therapy.

In Study C2301, PFS and OS in the PIK3CA-mutant cohort were the primary and key secondary endpoint respectively. The study was composed of two parallel cohorts, PIK3CA-mutant and PIK3CA-wild type. Cohorts were selected on tissue-based mutational assessment, but a circulating-DNA assessment was incorporated into the design. Tumour tissue had to be available for PIK3CA central mutational status determination. New tumour biopsy, preferably after the most recent progression or recurrence was favoured, but archival tissue was also accepted.

PIK3CA mutational status was assessed through analysis of hotspots located in the C2, helical and kinase domains of PI3K (corresponding to exons 7, 9 and 20 respectively), which are all critical for PI3K function (Zhao 2008). These hotspots, known to increase PI3K function, were anticipated to cover the majority of all the PIK3CA mutations identified in HR+ breast cancer patients according to the applicant. However, additional mutations of the PIK3CA genes have been reported in ER+ breast cancer patients. A new validated next generation sequencing (NGS) testing on additional mutations of baseline tissue samples is under development and patients with PIK3CA mutations outside the 11 used for enrolment into Study C2301 have been treated in earlier phase studies, showing apparently clinical benefit from alpelisib. In any case, the PIK3CA mutations included in Study C2301 (C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R or H1047Y) have been reflected under section 5.1 of the SmPC to allow the clinical physician to identify the mutation included in Study C2301.

As PIK3CA genomic studies are not included in routine clinical investigations, ctDNA tests could provide a good basis for selecting patients in a fast-practical way. The risk of false positive rates for plasma tests was clarified, being 8/572 (1.4%) with Novartis Clinical Trial Assay, 6/572 with the QIAGEN therascreen PIK3CA RGQ PCR Kit and reduced to 1/210 (0.5%) when the probability of assessing false positive rate for the plasma specimen type was assessed against a selected reference method of choice, which was a validated NGS assay. According to the applicant, the QIAGEN therascreen PIK3CA RGQ PCR Kit is CE-IVD marked and is available for testing at laboratories in the EU. Hence, the testing strategy proposed by the Applicant is acceptable.

The study was initially intended to analyse efficacy in the whole population set. However, non-clinical and clinical data from Study X2101 showed that patients with HR-positive, HER2-negative, PIK3CA non-mutant ABC derived much lower, if any, benefit from alpelisib than patients with mutant tumours. Similar observations were made in two large Phase III studies of buparlisib, a pan-PI3K inhibitor, in combination with fulvestrant (BELLE 2 & 3 trials; Di Leo, 2018). Furthermore, similar trends were observed in patients with

PIK3CA-mutant tumours assessed by ctDNA (Baselga, 2017; Di Leo, 2018) a finding also supported by data from the combination of alpelisib with letrozole or exemestane (Shah, 2015).

In total, 1442 patients (1439 women, 3 men) were screened and tested to establish PIK3CA mutation status while less than half of them were recruited (n=572 (39.7%)). In nearly all cases, the primary reason for not completing the screening phase was screen failure (92.8%). The identification of PIK3CA mutations led to more than 800 screening failures and of these, 500 cases were related to either a lack of identification of the mutation or a lack of adequate tissue. As the dropout rate was high, further insight into its causes was required. The applicant clarified that screen failure in Study C2301 is not equal to diagnostic test failure. Only 43 specimens did not yield a valid result from the *therascreen* PIK3CA RGQ PCR Kit. A relevant number of failures (377 subjects, 71.8%) were grouped as non-PIK3CA mutation status identified because they tested non-mutant, but the non-mutant cohort was already closed.

Investigator and patients were blinded to PIK3CA mutational status throughout the trial and the safety in both the PIK3CA mutant and non-mutant cohorts were reviewed by the DMC. Since the decision on using the PIK3CA non-mutant cohort as proof of concept was taken while the trial team was blinded, the amendment is unlikely to have compromised trial integrity. It should be also considered that given the effect of PI3K inhibitors on serum glucose levels and on the skin, it is doubtful that blinding was really effective for clinical researchers and study patients themselves but little else could have be done in that respect.

The amendments and protocol violations are deemed unlikely to have a relevant impact on the integrity of the study. More patients on alpelisib (20.7% (35 subjects)) received prohibited concomitant medications compared to patients on fulvestrant alone (14% (24 subjects)). The most frequently used prohibited medications were anti-infective and antiemetic agents (data not shown). This did not apparently affect efficacy but it is considered reflective of the increased toxicity with alpelisib.

The population enrolled in this study generally reflects the population of post-menopausal women with HR-positive, HER2-negative advanced breast cancer with disease progression on or after AI-based treatment, and as such is relevant to the intended target population.

In both study cohorts (with or without PIK3CA mutation), demographics and baseline disease characteristics, ECOG performance status, tumour burden and prior antineoplastic therapy were well balanced between the study arms.

Patients with symptomatic visceral disease or any disease burden making the patient ineligible for endocrine therapy were excluded from the study. Section 4.4 of the SmPC adequately reflects that the efficacy and safety of alpelisib have not been studied in patients with symptomatic visceral disease.

The choice of the comparator was discussed in light of the baseline characteristics of the patient population. Performance Status was 0 in two thirds of the trial patients and 1 in one third, reflecting a low tumour-burden population in which most oncologists would agree on further hormonal treatment rather than chemotherapy. However, 85.6% of the patients were considered to have endocrine-resistant disease and treatment options such as chemotherapy could have been an appropriate option in this setting. Primary endocrine resistance (*de novo* resistance) was observed in 13.2% of patients and secondary endocrine resistance (relapse/progression following an initial response) in 72.4% of patients. Nevertheless, fulvestrant monotherapy remains a therapeutic option for the population studied and it is acknowledged that endocrine resistance is not easy to apprehend in the clinical practice being more a time process than an event. Hence, the shortcomings of the trial design mimic real-world challenges. Also, the availability of another therapeutic option in a setting immediately before chemotherapy could represent a worthwhile alternative.

According to the wording of the study inclusion criterion "radiological or objective evidence of recurrence or progression during or after AI therapy", AI therapy was not required as last treatment regimen before study entry. AI treatment could have been given more than 12 months before progression of disease. Therefore, treatment with any endocrine-based therapy after AI therapy could be possible. In fact, 15.2% of the patients in the PIK3CA mutant cohort of Study C2301 received tamoxifen as last endocrine therapy before/when they had progression of their disease and one patient reported prior therapy with fulvestrant. However, this patient received only single fulvestrant monotherapy dose 29 days prior to being randomised to the alpelisib plus fulvestrant arm (the fulvestrant monotherapy treatment ended due to enrollment into Study C2301). In the phase I study X2101, 39 patients reported prior fulvestrant use (up to 180 days of treatment in 18 patients). Overall, although data are limited, those data suggest that no significant negative impact on efficacy was observed in those patients with heavily pre-treated advanced cancer with a PIK3CA mutation who had prior fulvestrant administration. Likewise, from a mechanistically perspective, there would not be any reason of such a possibility. Nevertheless, no firm conclusion can be drawn due to the limited number of patients with prior fulvestrant use. This has been reflected in the SmPC (see section 4.4 and 5.1).

A longer duration of last prior hormonal therapy was observed in the adjuvant as compared to the therapeutic (metastatic) setting. In the PIK3CA mutant cohort, duration of last hormonal therapy in the adjuvant setting for alpelisib arm was longer than for the placebo arm (51.8 vs 41.8 months). However, considering mean, Q1-Q3 and range, differences are not considered relevant.

Study C2301 allowed for the inclusion of males. However, the number of males included is very limited (1 patient). It is agreed that due to the rarity of this disease in males, it is simply not feasible to produce solid evidence of efficacy. However, the biological rationale and the overall treatment experience of male breast cancer so far are considered sufficient evidence for an extrapolation of the efficacy of alpelisib to this small subgroup (reflected in SmPC 5.1).

Alpelisib dose selection was based on a single first-in-human phase I clinical trial (Study X2101). Although the MTD was found to be 400 mg, the final dose selected for the phase 3 pivotal trial was chosen two dose-increase steps below (300 mg) based on PK and safety information, which is considered acceptable.

Efficacy data and additional analyses

PFS and OS in PIK3CA mutant cohort

The final PFS analysis was based on 232 events and a median follow-up time of 20.2 months corresponding to 61% of events in the alpelisib plus fulvestrant arm.

Study C2301 met its primary objective. Median PFS in patients with PIK3CA-mutations was prolonged by 5.3 months (from 5.7 to 11.0) for the alpelisib plus fulvestrant arm vs the fulvestrant arm (HR 0.65 95% CI 0.50, 0.85). Further strengthening the results, PFS curves in the Kaplan-Meier plot separated early and hold well its separation over time.

It could be questioned whether chemotherapy would have obtained better results than fulvestrant in this setting as the patients were mostly endocrine-resistant. As such using fulvestrant as a comparator may have distorted the results in favour of alpelisib. The poor performance of the control arm compared to other trials was explained by the large fraction of the study population being endocrine-resistant and as such having poorer prognosis.

Despite the above, the improvement of median PFS from 5.7 months in the placebo plus fulvestrant arm to 11.0 months in the alpelisib plus fulvestrant arm (HR=0.65) is considered clinically relevant in this setting.

Updated PFS data were provided with the DCO 30 September 2019. In the PIK3CA mutant cohort, a PFS event was reported for 123/169 (72.8%) patients in the alpelisib plus fulvestrant arm vs. 148/172 (86.0%) patients in the placebo plus fulvestrant arm. A HR of 0.64 (95% CI: 0.50, 0.81) was observed. Median PFS did not change with this update: median PFS was 11.0 months and 5.7 months in the alpelisib plus fulvestrant arm and the placebo plus fulvestrant arm, respectively. These results are in line with the previous ones.

As the rate of censoring was high, additional information about the early censored patients and their main reasons for censoring was provided. Early censoring for reason other than "ongoing without event" occurring up to the fourth tumour assessment were higher for alpelisib than placebo (10.7% vs 4.1%) (data not shown). Two additional supplementary analyses addressing the early censoring (censures in fourth tumour assessment) were performed: i) 5 patients who discontinued treatment due to physician decision, but with investigator comments indicating clinical progression were counted as having PFS events at the time of the last adequate assessment; ii) patients who withdrew consent were counted as having PFS event at the time of the last adequate assessment. These supplementary analyses showed concordant results (i) HR 0.66 95% CI 0.51, 0.86 ii) HR 0.71 95% CI 0.55, 0.91) with those presented in the primary analysis (data not presented).

Further details on patients' withdrawal were provided. Withdrawals were double in alpelisib arm in comparison with placebo (10 (6%) alpelisib vs 5 (3%) placebo). Five of them (4 in alpelisib arm and 1 in placebo) had AEs (alpelisib arm: 2 grade 3 hyperglycaemia, 1 grade 3 weight loss and 1 grade 2 rash; placebo arm: Grade 3 musculoskeletal pain). Nearly half of the withdrawals were in the first 28 days of treatment (5 in alpelisib and 2 in placebo). In the second supplementary analysis on early censoring (see previous paragraph), most of the patients who withdrew consent were counted as having PFS event at the time of the last adequate assessment. Two patients in alpelisib and 1 in placebo arm with withdrawn consent were not considered in that analysis because the withdrawals were after 224 days. HR in this supplementary analysis was similar to the primary analysis.

In another supplementary analysis considering discontinuation of either alpelisib/placebo and/or fulvestrant due to AE as treatment failure (PD), the HR of 0.89 (95% CI: 0.69, 1.14) was no longer statistically significant indicating no benefit of the addition of alpelisib if discontinuation due to AE is considered a negative outcome. However, the fact that patients who discontinue a drug prematurely due to toxicity thereby do not achieve the expected benefit is true for any drug. Only if these patients could be identified in advance, a loss of chance situation could be considered. In addition, the applicant performed a subgroup analysis on patients with or without discontinuation due to an AE. This analysis showed that median PFS for alpelisib plus fulvestrant patients was 11.0 months (HR: 0.67, 95% CI: 0.45, 1.02) for those who discontinued alpelisib treatment due to an AE and 9.4 months (HR: 0.64, 95%CI: 0.48, 0.86) for those who did not. Although the latter analysis could be biased, these results are pointing in the same direction as the ITT analysis.

The audit that compared the investigator-based PFS analysis with a central one conducted in randomly selected cases summing up 50% of the total sample was satisfactory and the prespecified thresholds to trigger a full 100% review were not met.

PFS subgroup analyses per investigator assessment by randomisation stratification factors showed a consistent treatment effect in favour of the alpelisib arm, irrespective of presence or absence of lung/liver metastases (see SmPC section 5.1).

Using a data cut-off date of 12 June 2018, PFS results for the subgroup of endocrine resistant patients (HR=0.64; 95% CI: 0.49, 0.85, n=292) and endocrine sensitive patients (HR=0.87; 95% CI: 0.35, 2.17, n=39) were in favour of the alpelisib plus fulvestrant arm. As the number of endocrine sensitive patients with a PIK3CA mutation was limited (n=39), these results should be interpreted with caution (reflected in SmPC section 5.1).

An interesting subgroup analysis refers to the genomic groups. It is reassuring that alpelisib plus fulvestrant had the same effect on all PIK3CA-mutant individuals, regardless of the mutation location (exon 9 or exon 20) or the three main mutations considered.

The OS results were not yet mature i.e. median OS not reached in the alpelisib arm and 26.9 months in the control arm. The event rate was 23.7% in the alpelisib arm and 30.2% in the control arm (92 events in total). Updated OS data was submitted with data cut-off of 30-Sep-2019. Percentage of events are 40.8% in alpelisib arm and 48.8% in placebo arm, median OS was reached for alpelisib (40.6 months) and placebo (31.2 months) arms. HR was 0.77 (95% CI 0.56, 1.06). OS results are still immature. In order to further investigate the efficacy of alpelisib in combination with fulvestrant in the target population, the MAH will submit by 31 August 2022 the final study report of the phase III randomized placebo-controlled study SOLAR-1 including interim and final analyses of overall survival (PAES, Annex II condition).

As a result of a GCP inspection, critical deficiencies were found in one of the investigational sites in Chile, thus, the inspectors recommended that these data were excluded from the analysis. Updated primary analysis of PFS and OS (using the original cut-off date of 12 Jun 2018) have been provided, excluding the four patients from this site in Chile, who were enrolled in the PIK3CA mutant cohort (data not shown). These analysis of PFS and OS were consistent with the original analysis. For PFS the HR was 0.63 (95% CI: 0.49, 0.80) and for OS the HR was 0.70 (95% CI: 0.46, 1.06).

Subgroup of patients previously treated with CDK4/6 inhibitors

Confirmatory trials should reflect the target population to be treated. CDK4/6 inhibitors in combination with endocrine therapy have become standard of care in the first-line treatment of HR-positive metastatic breast cancer. Thus, patients having received prior therapy with CDK 4/6 inhibitors is the most relevant population to reflect the target population. However, the total number of subjects pre-treated with a CDK4/6 inhibitor was predefined to be limited to 30% of the overall study population in the SOLAR-1 study. This was based on the concern at the time of the initial protocol, mid-2015, that prior treatment with a CDK4/6 inhibitor may impact the outcome of subsequent treatment with PI3K inhibitors compared to CDK4/6 inhibitor naive subjects.

The biological plausibility that an inconsistent response might be observed has been based on mechanistic considerations and clinical and pharmacological judgement, given the related pathways, unknown impact on clinical effects, and experience of unexpected interactions with prior treatments with anti-cancer agents acting on related pathways. The recent non-clinical data reporting the activation of the PI3K/AKT/mTOR pathway following resistance to CDK4/6 inhibitors and other *in vitro* observations (Jansen et al., 2017; O'Brien et al., 2019; O'Brien et al. 2019) seem to go against this judgment but the relevance of these findings in the clinical setting is unknown. Thus, these findings are not sufficient to disregard the biological plausibility of an inconsistent treatment effect.

In summary, it is of interest to verify that the conclusions of therapeutic efficacy apply consistently to the subgroup of the clinical trial population consisting of patients pre-treated with CDK 4/6 inhibitors because the confirmatory trial does not reflect the target population of the claimed indication which mainly consists of

patients pre-treated with CDK 4/6 inhibitors; and there is biological plausibility for an inconsistent treatment effect in the patients pre-treated with CDK 4/6 inhibitors.

To this end, the available clinical data are scarce as this was only a small subgroup in the confirmatory study. The actual number of patients included who had prior treatment with CDK 4/6 inhibitors was 20 patients, 9 receiving alpelisib. The limited sample size does not allow drawing any firm conclusions. Regarding the ORR, it was noted that no responses were observed in this specific group of patients.

During the review, the Applicant presented supportive data from cohort A of the BYLieve study, which was a single-arm, non-comparative cohort study that included 121 patients previously exposed to CDK4/6 inhibitors. The ORR in patients with measurable disease was 21% and the DOR was 6.6 months (95%CI: 4.3; NE), whereas in the PIK3CA mutant cohort within the SOLAR-1 study, in patients with measurable disease, the ORR in the treatment arm with the combination of alpelisib plus fulvestrant regardless of the prior treatment (n=169) was 35.7% (95%CI: 27.4, 44.7) and the DOR 12.6 months (95%CI: 8.5, 18.5). However, due to the design of the study BYLieve it is not possible to isolate the contribution of fulvestrant.

Overall, available efficacy results, if anything, would be indicative of low activity (17.4% ORR in the BYLieve study, cohort A; point estimate of 3.7 months difference in median PFS in the SOLAR-1 study). This is in agreement with the SAG that concluded that "overall the data available are too sparse to establish efficacy in this population for which limited but established treatment options exist" (see further below). In conclusion, there are insufficient clinical data to establish efficacy in patients pre-treated with CDK 4/6 inhibitors. The indication has been restricted to patients previously treated with endocrine therapy as monotherapy.

PFS and OS in PIK3CA-wild type cohort

As expected for a PI3KCA inhibitor, PFS results indicate a lack of clinical efficacy in PI3KCA wild-type tumours. OS data were immature. No further statistical testing of OS data was planned. However, two descriptive updates using the data cut-offs of 23-Dec-2016 and 30-Sep-2019 were provided. With the last DCO, percentage of events were 51.3% in alpelisib arm and 50.9% in placebo arm, and the median OS was reached for the alpelisib (37.3 months 95% CI: 27.89, 45.37) and placebo (34.3% 95% IC: 26.81, 42.41) arms. HR was 0.92 (95% CI 0.64, 1.33). These last updated results, with an acceptable maturity, are in line with previous analyses.

Other secondary endpoints

A perhaps unexpected finding was the effect of the alpelisib-fulvestrant combination on tumour response, with an ORR 2.6 times better than fulvestrant plus placebo and a significant fraction of responding patients showing >30% tumour shrinkage in the waterfall plots.

The ORR was improved clinically significantly compared to the control arm ORR 12.8% (SD 36.6% and Non-CR/non-PD 14.5%). Stabilization of the disease is clinically meaningful as this prolongs the time on an endocrine-based regimen and consequently a postponement of use of more toxic anticancer treatments such as chemotherapy.

In clinical practice, chemotherapy is sometimes chosen over endocrine treatment on the grounds of a more likely response or faster volume reduction when the disease bulk is related to symptoms or is felt as an immediate threat for organ function. The ORR results may be reassuring for practising oncologists indecisive between targeted treatment vs conventional chemotherapy in bulky ABC cases when a volumetric response is needed.

Duration of response was determined in a small sample size in the placebo arm for an adequate treatment comparison (n=9). Although difficult to assess from this data, but the median duration of response of 12.6 months in the responding patients is considered clinically meaningful and in line with the PFS results. Firm conclusions are not possible due to the small sample sizes.

Time to response results are clinically meaningful and reinforce the ORR conclusions.

No detrimental effects were observed in PFS2. However, results were initially not mature. Two updated PFS2 data were provided, which were all consistent. In the last updated data, percentage of events were 62.7% in alpelisib arm and 69.2% in placebo arm in the mutant cohort, thus, data can now be considered relatively mature and supportive of the initial conclusion.

No indication of a detrimental effect on ECOG PS or Global Health Status with alpelisib was observed either. This was also confirmed with recent updated data; however, since the safety profile is considered to have unblinded the investigators, the PRO data could be biased and should not be included in the SmPC.

Additional expert consultations

During the CHMP meeting on 27 February 2020, the CHMP concluded that the SAG Oncology should be consulted for their views on whether efficacy in patients previously treated with CDK 4/6 inhibitors can be considered as established.

The SAG Oncology meeting was held on 15 April 2020. The following questions were addressed and the outcome of the discussion is presented below.

1. **The proposed indication wording includes those patients previously treated with CDK 4/6 inhibitors. However, available clinical data are too sparse to independently establish efficacy in such patients.**

   Does the SAG consider that available data allow for the extrapolation of a clinically meaningful benefit of alpelisib in combination with fulvestrant to patients previously treated with CDK 4/6 inhibitors?

   In the overall population of the SOLAR-1 study, alpelisib+fulvestrant was associated with a modest effect on PFS (5.3 months difference in median PFS compared fulvestrant+placebo; HR [95% CI] = 0.65 [0.50, 0.85]) in patients with a PIK3CA mutation progressing on endocrine-based therapy.(1) Currently, no important clinical effect has been observed in term of other important endpoints like OS (86% information fraction) and HR-QoL.

   For comparison, possible strategies in patients that progressed on aromatase inhibitor therapy (although supporting results are based on trials not selected for PIK3CA mutation), include everolimus+fulvestrant (5.2 months difference in median PFS compared fulvestrant+placebo; HR [95% CI] = 0.61 [95% CI, 0.40 to 0.92]) (2) and capecitabine, based on the "PEARL" trial where after a median 17.64 months of follow-up, median PFS was 7.4 versus 9.4 months with palbociclib/fulvestrant v. capecitabine, respectively. (2019 San Antonio Breast Cancer Symposium).

   Concerning the CDK 4/6 inhibitor-pre-treated population, all experts agreed that another therapeutic option would be welcome for patients that progressed following previous treatment with CDK 4/6 inhibitors. This clinical situation is quite relevant given that CDK 4/6 inhibitors are considered as the

treatment of choice in combination with hormone therapy to treat hormone receptor-positive, HER2-negative metastatic breast cancer.

The SAG unanimously agreed that overall the data available are too sparse to establish efficacy in this population for which limited but established treatment options exist.[1] Indeed, optimality of the fulvestrant-alone control arm was questioned when only a small minority of patients (about 12%) had disease that could be considered "endocrine sensitive". Although fulvestrant-alone is a suitable choice in some patients, there are other options available, including some that may have a larger effect on PFS (see above).

If anything, the available clinical data from the trial would be indicative of low activity (17.4% ORR in the BYLieve study, cohort A; point estimate of 3.7 months difference in median PFS in the SOLAR-1 study and non-statistically significant difference in PFS).

Admittedly, no strong signal of a detrimental effect was evident in patients previously treated with CDK 4/6 inhibitors, but the interval estimates are so wide that a detrimental effect cannot be ruled out with sufficient certainty (the upper 95% confidence limit was 1.36 and 2.06, for PFS and OS HR, respectively, in the SOLAR-1 study). Although it is difficult to compare across trials and different population selection criteria, and acknowledging the many uncertainties, there are concerns that the evidence for benefit of available treatment options like everolimus combinations and capecitabine is more convincing than for alpelisib+fulvestrant for which there are very few data (N=9 patients treated with alpelisib+fulvestrant in the SOLAR-1 trial).

The SAG discussed the possibility to substitute data in patients previously treated with CDK 4/6 inhibitors using external data. The current external comparisons presented on the basis of the BYLieve study were of limited value given the small numbers of patients treated, the highly selected population, and the limited number of matching variables used.

A prospective randomized-controlled clinical trial is considered feasible in this population and would be expected to provide the most convincing results to address this question. However, given the large number of patients treated with the product, there would also be merit in exploring the effect in patients previously treated with CDK 4/6 inhibitors by collecting real-world data and conducting larger matched analyses using an adequate set of variables to maximise comparability against standard of care. If such analysis could be sufficient and convincing to establish efficacy will depend on the data and results.

The SAG also commented on other aspects related to this clinical trial, namely, the fact that fresh tissue at the time of enrolment was only available for about 8% of patients. Although the good correlation with circulating tumour DNA was noted, lack of fresh tissue limits the ability to conduct further biomarker analyses, which should be a standard objective of any modern drug development according to EMA guidelines. Nevertheless, the ongoing analyses based on archival tissues should be submitted to allow better understanding of the impact of genomic alterations on response.

The SAG also commented on the short duration of follow-up in terms of safety, and the need to assess if toxicity in the clinical setting can be managed as well as in clinical trials, especially in the

[1] One expert, classified as "expert witness" based on declared interests, stated that based on personal experience (durable responses in some patients), the non-clinical data and rationale, and the scant but coherent clinical data from SOLAR-1 and, in particular, the supportive results from the BYLieve study, that overall evidence was sufficient for extrapolating the effect to the CDK 4/6 inhibitor-positive population. However, as per the EMA policy on conflict of interests, experts that participate as "expert witness" do not participate in the conclusions. Therefore, this view was not included in the answers from the SAG.

context of an expected older target population with a risk for more frequent side effects (e.g., gastrointestinal toxicity).

2. **If further data on the efficacy of Piqray in CDK4/6 experienced patients are considered warranted, before or after marketing authorisation what might be a feasible and informative study design to establish clinical benefit in this population?**

   A prospective randomized-controlled clinical trial v. an appropriate control (e.g., investigator choice) is considered feasible in this population and would be expected to provide the most convincing results to address this question. Stratification between progression on v. relapsing after CDK 4/6 inhibitor should be considered.

   Given the large number of patients treated with the product, there would also be merit in exploring the effect in patients previously treated with CDK 4/6 inhibitors by collecting real-world data and conducting larger matched analyses using an adequate set of variables to maximise comparability against standard of care. Appropriate plans and protocols for such analyses should be submitted.

   Further molecular analyses based on fresh tissue prior to treatment and upon progression should be considered for a better selection of the target population and to elucidate mechanisms of resistance.

2.5.4. Conclusions on the clinical efficacy

Overall, the use of the combination of alpelisib and fulvestrant in the mutant cohort has shown to delay the tumour progression, with no indication of detrimental effect on overall survival and satisfactory pharmacodynamic activity. No PFS benefit was observed in patients whose tumours did not have a PIK3CA tissue mutation (see SmPC section 5.1).

However, the efficacy of alpelisib has not been established in the subpopulation of patients who have received prior CDK4/6 inhibitors and the indication has been restricted to exclude this group.

In conclusion, the efficacy is considered established for alpelisib in combination with fulvestrant for patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

As OS results are still immature, the CHMP considers the following measure necessary to address issues related to efficacy:

The applicant is required to conduct a post-authorisation efficacy study (PAES) in order to further investigate the efficacy and long-term safety of alpelisib in combination with fulvestrant in postmenopausal women, and men, with hormone receptor positive, human epidermal growth factor receptor 2 negative, advanced breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy. The applicant should submit the final study report of the phase III randomized placebo-controlled study SOLAR-1 including interim and final analyses of overall survival by 31 August 2022.

2.6. Clinical safety

Patient exposure

Safety evaluation is based on data from 825 patients treated in three clinical studies. The primary focus is on data from 571 patients treated in the randomised, double-blind, placebo-controlled Phase III Study C2301 in subjects with HR-positive, HER2-negative ABC, with 284 patients in the alpelisib plus fulvestrant group and 287 patients in the placebo plus fulvestrant group. In addition, 167 patients were exposed to single-agent alpelisib and 87 patients were exposed to alpelisib in combination with fulvestrant in the dose-finding studies X2101 and X1101.

Table 56. Overview of clinical studies that contributed safety data

Study / Phase	Population	FPFV/ LPLV Study status	Treatment dosing schedule	Number of subjects included in safety analyses
Alpelisib in combination with fulvestrant				
C2301 / Phase III Registration study	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease progressed on or after AI treatment. Subjects were enrolled into one of two cohort (PIK3CA mutant, PIK3CA non-mutant)	23-Jul-2015 / 12-Jun-2018* Study is ongoing	Alpelisib 300 mg or placebo once daily plus fulvestrant 500 mg IM on Day 1 and 15 of Cycle 1 and on Day 1 ± 3 days of subsequent 28-day cycles	**Total: 571** Alpelisib plus fulvestrant: 284 Placebo plus fulvestrant: 287 **By PIK3CA mutation status:** **PIK3CA mutant: 340** Alpelisib plus fulvestrant: 169 Placebo plus fulvestrant: 171 **PIK3CA non-mutant: 231** Alpelisib plus fulvestrant: 115 Placebo plus fulvestrant: 116
X2101 / Phase IA (Combination) Dose escalation and expansion parts	Postmenopausal women with HR-positive, HER2-negative breast cancer	05-Oct-2010 / 22-Mar-2017 Study is ongoing	**Escalation part:** Alpelisib 300, 350, or 400 mg once daily plus fulvestrant 500 mg IM on Day 1 and 15 of Cycle 1 and on Day 1 ± 3 days of subsequent 28-day cycles **Expansion part:** Alpelisib 400 mg once daily plus fulvestrant 500 mg IM on Day 1 and 15 of Cycle 1 and on Day 1 ± 3 days of subsequent 28-day cycles	**Total: 87** 300 mg: 9; 350 mg: 8; 400 mg: 70 By PIK3CA mutation status: PIK3CA altered: 52 PIK3CA wild-type: 33 PIK3CA alteration unknown: 2
Alpelisib monotherapy				
X2101 / Phase IA (Single agent) Dose escalation part	Adult subjects with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene	05-Oct-2010 / 22-Mar-2017 Study is ongoing	**Escalation part:** Alpelisib 30, 60, 90, 180, 270, 300, 350, 400, or 450 mg once daily, or 120, 150, or 200 mg twice daily **Expansion part:** Alpelisib 400 mg once daily	**Total: 134** 30 mg: 1; 60 mg: 3; 90 mg: 6; 180 mg: 6, 270 mg: 4, 300 mg: 8; 350 mg: 6; 400 mg: 65; 450 mg: 9; 120 mg b.i.d.: 5; 150 mg b.i.d.: 15; 200 mg b.i.d.: 6
X1101 / Phase I Dose escalation and expansion parts	Adult subjects with advanced solid malignancies (Japan only).	22-Sep-2011 / 25-Nov-2015 Completed	**Escalation part**: Alpelisib 90, 180, 270, 350, or 400 mg once daily **Expansion part:** Alpelisib 350 mg once daily	**Total: 33** 90 mg: 3; 180 mg: 4; 270 mg: 5; 350 mg: 14; 400 mg: 7
* Cut-off date for safety analyses				

As of the 12 June 2018 data cut-off, exposure to the alpelisib plus fulvestrant combination was 2847.3 subject-months and 2530.4 subject-months to placebo plus fulvestrant The median duration of exposure to study treatment was longer in the alpelisib plus fulvestrant group (8.2 months) compared to the placebo plus fulvestrant treatment group (5.6 months). In the alpelisib plus fulvestrant treatment group, exposure to fulvestrant was longer than to alpelisib (median 8.2 vs. 5.5 months), as patients who discontinued alpelisib for reasons other than disease progression were allowed to continue on fulvestrant.

The median relative dose intensities to alpelisib and placebo were 83.7% and 100%, respectively. Dose adjustments (interruptions and/or reductions) were allowed for alpelisib to manage treatment-emergent toxicities. No dose modification was permitted for fulvestrant; however, dose interruption was allowed.

Updated safety data from Study C2301 (cut-off date of 20 Oct 2018 and 30 Sep 2019) are also presented below.

Table 57. Duration of exposure to study drug - Study C2301 (Safety set)

	Original MAA DCO date: 12-Jun-2018						90-day Safety Update DCO date: 20-Oct-2018						Interim OS analysis DCO date: 30-Sep-2019					
	Alpelisib plus fulvestrant N = 284			Placebo plus fulvestrant N = 287			Alpelisib plus fulvestrant N = 284			Placebo plus fulvestrant N = 287			Alpelisib plus fulvestrant N = 284			Placebo plus fulvestrant N = 287		
	Alp	Fulv	Over	Plac	Fulv	Over	Alp	Fulv	Over	Plac	Fulv	Over	Alp	Fulv	Over	Plac	Fulv	Over
Total subjects (%)	99.6[1]	100	100	99.7[1]	100	100	99.6[1]	100	100	99.7[1]	100	100	99.6[1]	100	100	99.7[1]	100	100
Duration of exposure (mo)																		
Mean	8.0	10.0	10.0	8.4	8.8	8.8	8.6	10.8	10.8	9.0	9.4	9.4	9.7	12.3	12.3	9.7	10.4	10.4
Median	5.5	8.2	8.2	5.6	5.6	5.6	5.5	8.2	8.2	5.6	5.6	5.6	5.5	8.2	8.2	5.6	5.6	5.6
Min-max	0.0-30.8	0.4-30.8	0.4-30.8	0.0-30.1	0.5-30.1	0.5-30.1	0.0-35.1	0.4-35.1	0.4-35.1	0.0-34.4	0.5-34.4	0.5-34.4	0.0-44.7	0.4-44.7	0.4-44.7	0.0-45.7	0.5-45.7	0.5-45.7
Exposure categories[2] (%)																		
< 1 month	13.4	5.3	5.3	4.5	3.8	3.1	13.4	5.3	5.3	4.5	3.8	3.1	13.4	5.3	5.3	4.5	3.8	3.1
≥ 1 month	86.6	94.7	94.7	95.5	96.2	96.9	86.6	94.7	94.7	95.5	96.2	96.9	86.6	94.7	94.7	95.5	96.2	96.9
≥ 2 months	69.4	86.6	86.6	75.6	77.7	77.7	69.0	86.6	86.6	75.6	77.7	77.7	69.0	86.6	86.6	75.6	77.7	77.7
≥ 3 months	65.8	81.3	81.3	65.9	66.6	66.9	65.5	81.3	81.3	65.9	66.6	66.9	65.5	81.3	81.3	65.9	66.6	66.9
≥ 4 months	58.1	71.8	72.2	53.7	56.1	56.1	57.7	71.8	72.2	53.7	56.1	56.1	57.7	71.8	72.2	53.7	56.1	56.1
≥ 6 months	45.8	59.2	59.2	48.1	49.1	49.1	45.8	59.2	59.2	48.1	49.1	49.1	45.8	59.2	59.2	48.1	49.1	49.1
≥ 12 months	27.8	35.6	35.6	27.2	28.9	28.9	28.2	35.9	35.9	27.9	29.6	29.6	28.2	35.9	35.9	27.9	29.6	29.6
≥ 18 months	14.1	18.3	18.3	15.7	16.7	16.7	17.6	23.2	23.2	19.2	19.5	20.2	18.7	24.6	24.6	20.6	21.6	21.6
≥ 24 months	-	-	-	-	-	-	-	-	-	-	-	-	12.7	16.5	16.9	11.8	13.2	13.2
≥ 30 months	-	-	-	-	-	-	-	-	-	-	-	-	8.5	12.3	12.3	5.9	8.0	8.0
≥ 36 months	-	-	-	-	-	-	-	-	-	-	-	-	3.5	5.6	5.6	3.1	3.8	3.8
≥ 42 months	-	-	-	-	-	-	-	-	-	-	-	-	0.4	0.4	0.4	0.7	1.0	1.0

Alp Alpelisib; Fulv Fulvestrant; Over Overall (corresponds to duration of study treatment); Plac Placebo

[1] One patient was not dispensed alpelisib and one patients was not dispensed placebo

[2] Exposure categories beyond 18 months are only provided for the most recent DCO date

Source: Study C2301-Table 14.3-1.3, [SCS Appendix 3-Table 14.3-1.3su], Appendix 1-Table 14.3-1.3

Table 58. Subject disposition - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant	Placebo plus fulvestrant	Alpelisib 300 mg plus fulvestrant	Placebo plus fulvestrant
	N=284	N=287	N=284	N=287
	n (%)	n (%)	n (%)	n (%)
Subjects treated				
Treatment ongoing*	47 (16.5)	36 (12.5)	25 (8.8)	16 (5.6)
End of treatment	237 (83.5)	251 (87.5)	259 (91.2)	271 (94.4)
Primary reason for end of treatment				
Progressive disease	181 (63.7)	217 (75.6)	200 (70.4)	236 (82.2)
Subject/guardian decision	22 (7.7)	10 (3.5)	25 (8.8)	10 (3.5)
Adverse event	14 (4.9)	4 (1.4)	14 (4.9)	4 (1.4)
Physician decision	11 (3.9)	10 (3.5)	11 (3.9)	11 (3.8)
Protocol deviation	5 (1.8)	6 (2.1)	5 (1.8)	6 (2.1)
Death	4 (1.4)	4 (1.4)	4 (1.4)	4 (1.4)
Post treatment follow-up phase				
Not applicable^	218 (76.8)	242 (84.3)	239 (84.2)	261 (90.9)
Subjects no longer being followed for post treatment follow-up	14 (4.9)	8 (2.8)	18 (6.3)	10 (3.5)
Subjects continuing to be followed for post treatment follow-up	5 (1.8)	1 (0.3)	2 (0.7)	0
Primary reason for post treatment follow-up discontinuation				
Progressive disease	10 (3.5)	4 (1.4)	12 (4.2)	4 (1.4)
Subject/guardian decision	3 (1.1)	2 (0.7)	5 (1.8)	2 (0.7)
Physician decision	1 (0.4)	0	1 (0.4)	1 (0.3)
Death	0	2 (0.7)	0	2 (0.7)
Lost to follow-up	0	0	0	1 (0.3)

* Subjects ongoing at the time of the cut-off (20-Oct-2018 for safety update 1, 30-Sep-2019 for safety update 2)

^ Subjects who discontinued due to progressive disease at end of treatment evaluation, or who did not continue into the next phase or who continued into survival follow-up after end of treatment evaluation.

Source: SCS Appendix 3-Table 1-1.1.1su, [SCS Appendix 5-Table 1-1.1.1su2]

Adverse events

Table 59. Overview of adverse events – Study C2301 (Safety set)

	Original MAA DCO date: 12-Jun-2018				90-day Safety Update DCO date: 20-Oct-2018				Interim OS analysis DCO date: 30-Sep-2019			
	Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287		Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287		Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Category	%	%	%	%	%	%	%	%	%	%	%	%
Adverse events	99.3	76.1	92.0	35.5	99.3	76.8	92.3	35.9	99.3	77.5	92.7	36.6
Treatment related	93.0	65.5	63.1	11.1	93.3	66.2	63.4	11.1	93.3	66.9	63.8	11.8
SAEs	34.9	28.9	16.7	15.0	35.2	28.9	17.1	15.3	36.6	29.9	18.8	16.7
Treatment related	22.5	18.7	1.7	1.4	22.5	18.3	1.7	1.4	22.9	18.7	1.7	1.4
Fatal SAEs	1.1	1.1	1.0	1.0	1.1	1.1	1.0	1.0	1.4	1.4	1.4	1.4
Treatment related	0.4	0.4	0	0	0.4	0.4	0	0	0.4	0.4	0	0
AEs leading to discontinuation	25.0	13.0	4.5	3.8	25.4	13.0	4.5	3.1	26.1	13.0	5.6	3.8
Treatment related	21.8	10.2	3.1	2.8	22.2	10.2	3.1	2.4	22.9	10.2	3.8	2.8
AEs leading to dose adjustment/interruption	78.5	62.7	22.6	14.3	78.9	63.4	22.3	13.9	79.2	63.7	23.0	14.6
AEs requiring additional therapy	97.5	65.1	70.0	24.7	97.5	66.2	70.7	24.7	97.9	66.9	70.7	25.8

Source: Study C2301-Table 12-4, SCS Appendix 3-Table 14.3.1-1.1su, Table 14.3.1-1.2su, Table 14.3.1-1.3su, Table 14.3.1-1.6su, Table 14.3.1-1.7su, Table 14.3.1-1.8su, Table 14.3.1-1.9su, Table 14.3.1-1.10su, Table 14.3.1-1.11su, Appendix 1-Table 14.3.1-1.1, Table 14.3.1-1.2, Table 14.3.1-1.3, Table 14.3.1-1.6, Table 14.3.1-1.7, Table 14.3.1-1.8, Table 14.3.1-1.9, Table 14.3.1-1.10, Table 14.3.1-1.11

Table 60. Adverse events (at least 10% all grades in either treatment group) by preferred term and maximum grade – Study C2301 (Safety set)

	Original MAA DCO date: 12-Jun-2018				90-day Safety Update DCO date: 20-Oct-2018				Interim OS analysis DCO date: 30-Sep-2019			
	Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287		Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287		Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287	
Preferred term	All grades %	Grade 3/4 %	All grades %	Grade 3/4 %	All grades %	Grade 3/4 %	All grades %	Grade 3/4 %	All grades %	Grade 3/4 %	All grades %	Grade ¾ %
Total	**99.3**	**76.1**	**92.0**	**35.5**	**99.3**	**76.8**	**92.3**	**35.9**	**99.3**	**77.5**	**92.7**	**36.6**
Hyperglycaemia	63.7	36.6	9.8	0.7	64.1	37.0	9.8	1.0	64.8	37.0	9.4	1.0
Diarrhoea	57.7	6.7	15.7	0.3	58.5	7.0	16.4	0.7	59.5	7.0	16.4	0.7
Nausea	44.7	2.5	22.3	0.3	45.4	2.5	22.6	0.3	46.8	2.8	22.6	0.3
Rash	35.6	9.9	5.9	0.3	35.6	9.5	6.6	0.3	36.3	9.9	7.0	0.3
Decreased appetite	35.6	0.7	10.5	0.3	35.6	0.7	10.5	0.3	35.9	0.7	10.5	0.3
Vomiting	27.1	0.7	9.8	0.3	27.8	0.7	10.1	0.3	28.5	0.7	10.1	0.3
Weight decreased	26.8	3.9	2.1	0	26.8	4.2	2.1	0	27.8	5.3	2.4	0
Fatigue	24.3	3.5	17.1	1.0	24.6	3.5	17.4	1.0	25.0	3.5	17.8	1.0
Stomatitis	24.6	2.5	6.3	0	24.6	2.5	7.3	0	25.0	2.5	7.0	0
Asthenia	20.4	1.8	12.9	0	21.1	2.1	13.2	0	22.2	2.5	13.6	0
Alopecia	19.7	0	2.4	0	20.1	0	2.4	0	20.4	0	2.4	0
Headache	17.6	0.7	13.2	0	18.0	0.7	13.2	0	19.0	0.7	13.2	0
Mucosal inflammation	18.3	2.1	1.0	0	18.7	2.1	1.4	0	18.7	2.1	1.4	0
Pruritus	18.0	0.7	5.6	0	18.3	0.7	6.3	0	18.7	2.1	1.4	0
Pyrexia	14.4	0.7	4.9	0.3	14.8	0.7	5.2	0.3	15.8	0.7	5.6	0.3
Oedema peripheral	14.4	0	4.5	0	14.8	0	4.9	0	15.8	0	4.9	0
Dry skin	14.8	0	3.5	0	15.1	0	3.5	0	15.5	0	3.5	0
Back pain	13.7	1.8	12.9	1.4	14.1	1.8	13.2	1.4	14.8	1.8	13.9	1.4
Rash maculo-papular	14.1	8.8	1.7	0.3	14.1	8.8	1.4	0	14.1	8.8	1.4	0
Dysgeusia	16.5	0	3.5	0	16.5	0	3.5	0	13.7	0	2.8	0
Arthralgia	11.3	0.4	16.4	1.0	11.6	0.4	17.4	1.0	13.0	0.4	17.8	1.0
Cough	9.9	0.4	9.4	0	10.6	0.4	9.4	0	12.7	0.4	9.8	0
Abdominal pain	11.6	1.4	7.0	1.0	12.0	1.4	7.3	1.4	12.3	1.4	7.7	1.4
Dyspepsia	11.3	0	5.6	0	11.3	0	5.9	0	11.6	0	5.9	0
Blood creatinine increased	10.2	1.8	1.4	0	10.2	1.8	1.4	0	11.3	1.8	1,4	0
Aspartate aminotransferase increased	9.5	2.1	5.2	1.7	10.9	2.8	6.3	2.1	10.9	2.8	6.3	2.1
Anaemia	9.2	3.5	4.9	1.0	10.6	4.2	7.0	1.4	10.6	4.2	7.0	1.4
Dry mouth	9.5	0.4	4.2	0	10.2	0.4	4.2	0	10.6	0.4	4.5	0
Dyspnoea	8.5	0.4	10.5	2.1	8.5	0.4	10.5	2.1	10.2	1.1	11.8	2.1
Urinary tract infection	10.2	0.7	5.2	1.0	10.2	0.7	5.2	1.0	10.2	0.7	5.6	1.0
Constipation	7.7	0	12.5	0.3	8.1	0	12.9	0.3	8.1	0	12.9	0.3

Source: Study C2301-Table 14.3.1-1.1, SCS Appendix 3-Table 14.3.1-1.1su, Appendix 1-Table 14.3.1-1.1

Table 61. Grade 3 and grade 4 adverse events (>1% grade 3 or grade 4 in either treatment group) by preferred term and maximum grade - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off				Safety update 2: 30-Sep-2019 cut-off			
	Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287		Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287	
Preferred term	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
-Total	185 (65.1)	33 (11.6)	87 (30.3)	16 (5.6)	185 (65.1)	35 (12.3)	88 (30.7)	17 (5.9)
Hyperglycaemia	94 (33.1)	11 (3.9)	2 (0.7)	1 (0.3)	94 (33.1)	11 (3.9)	2 (0.7)	1 (0.3)
Rash	27 (9.5)	0	1 (0.3)	0	28 (9.9)	0	1 (0.3)	0
Rash maculo-papular	25 (8.8)	0	0	0	25 (8.8)	0	0	0
Diarrhoea	20 (7.0)	0	2 (0.7)	0	20 (7.0)	0	2 (0.7)	0
Weight decreased	12 (4.2)	0	0	0	15 (5.3)	0	0	0
Anaemia	11 (3.9)	0	3 (1.0)	0	12 (4.2)	0	4 (1.4)	0
Hypertension	12 (4.2)	1 (0.4)	9 (3.1)	0	12 (4.2)	1 (0.4)	9 (3.1)	0
Lipase increased	13 (4.6)	2 (0.7)	8 (2.8)	3 (1.0)	12 (4.2)	3 (1.1)	8 (2.8)	3 (1.0)
Gamma-glutamyltransferase increased	10 (3.5)	1 (0.4)	11 (3.8)	3 (1.0)	11 (3.9)	1 (0.4)	14 (4.9)	3 (1.0)
Fatigue	10 (3.5)	0	3 (1.0)	0	10 (3.5)	0	3 (1.0)	0
Hypokalaemia	9 (3.2)	3 (1.1)	1 (0.3)	0	10 (3.5)	3 (1.1)	1 (0.3)	0
Alanine aminotransferase increased	7 (2.5)	0	7 (2.4)	0	8 (2.8)	1 (0.4)	7 (2.4)	0
Nausea	7 (2.5)	0	1 (0.3)	0	8 (2.8)	0	1 (0.3)	0
Aspartate aminotransferase increased	6 (2.1)	0	5 (1.7)	1 (0.3)	7 (2.5)	1 (0.4)	5 (1.7)	1 (0.3)
Asthenia	6 (2.1)	0	0	0	7 (2.5)	0	0	0
Stomatitis	7 (2.5)	0	0	0	7 (2.5)	0	0	0
Hyponatraemia	6 (2.1)	2 (0.7)	5 (1.7)	0	6 (2.1)	2 (0.7)	5 (1.7)	0
Mucosal inflammation	6 (2.1)	0	0	0	6 (2.1)	0	0	0
Amylase increased	5 (1.8)	1 (0.4)	7 (2.4)	0	5 (1.8)	1 (0.4)	7 (2.4)	0
Back pain	5 (1.8)	0	4 (1.4)	0	5 (1.8)	0	4 (1.4)	0
Blood creatinine increased	5 (1.8)	0	0	0	5 (1.8)	0	0	0
Osteonecrosis of jaw	4 (1.4)	0	2 (0.7)	0	5 (1.8)	0	3 (1.0)	0
Abdominal pain	4 (1.4)	0	4 (1.4)	0	4 (1.4)	0	4 (1.4)	0
Lymphocyte count decreased	4 (1.4)	1 (0.4)	1 (0.3)	0	4 (1.4)	1 (0.4)	1 (0.3)	0
Neutropenia	4 (1.4)	1 (0.4)	1 (0.3)	2 (0.7)	4 (1.4)	1 (0.4)	1 (0.3)	2 (0.7)
Pleural effusion	3 (1.1)	0	5 (1.7)	0	4 (1.4)	0	5 (1.7)	0
Acute kidney injury	3 (1.1)	0	1 (0.3)	0	3 (1.1)	0	1 (0.3)	0
Hypophosphataemia	3 (1.1)	0	1 (0.3)	0	3 (1.1)	0	1 (0.3)	0
Lymphopenia	1 (0.4)	1 (0.4)	2 (0.7)	0	3 (1.1)	1 (0.4)	2 (0.7)	0
Pneumonia	3 (1.1)	0	4 (1.4)	1 (0.3)	3 (1.1)	0	4 (1.4)	1 (0.3)
Pulmonary embolism	2 (0.7)	0	4 (1.4)	0	3 (1.1)	0	4 (1.4)	0
Dyspnoea	1 (0.4)	0	5 (1.7)	1 (0.3)	2 (0.7)	1 (0.4)	5 (1.7)	1 (0.3)
Blood alkaline phosphatase increased	0	0	5 (1.7)	0	0	0	5 (1.7)	0
Hyperkalaemia	0	0	5 (1.7)	0	0	0	5 (1.7)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-1.1su, [SCS Appendix 5-Table 14.3.1-1.1]

Table 62. Treatment-related adverse events (at least 10% in either treatment group) by preferred term and maximum grade - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off				Safety update 2: 30-Sep-2019 cut-off			
	Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287		Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	265 (93.3)	188 (66.2)	182 (63.4)	32 (11.1)	265 (93.3)	190 (66.9)	183 (63.8)	34 (11.8)
Hyperglycaemia	171 (60.2)	96 (33.8)	17 (5.9)	0	173 (60.9)	96 (33.8)	16 (5.6)	0
Diarrhoea	111 (39.1)	16 (5.6)	22 (7.7)	1 (0.3)	114 (40.1)	16 (5.6)	21 (7.3)	1 (0.3)
Nausea	101 (35.6)	4 (1.4)	41 (14.3)	0	105 (37.0)	5 (1.8)	41 (14.3)	0
Rash	88 (31.0)	26 (9.2)	13 (4.5)	1 (0.3)	88 (31.0)	27 (9.5)	13 (4.5)	1 (0.3)
Decreased appetite	81 (28.5)	1 (0.4)	13 (4.5)	0	82 (28.9)	1 (0.4)	13 (4.5)	0
Fatigue	59 (20.8)	8 (2.8)	33 (11.5)	0	60 (21.1)	8 (2.8)	33 (11.5)	0
Stomatitis	59 (20.8)	7 (2.5)	11 (3.8)	0	59 (20.8)	7 (2.5)	11 (3.8)	0
Vomiting	52 (18.3)	1 (0.4)	10 (3.5)	0	54 (19.0)	1 (0.4)	10 (3.5)	0
Weight decreased	44 (15.5)	6 (2.1)	3 (1.0)	0	46 (16.2)	8 (2.8)	3 (1.0)	0
Asthenia	43 (15.1)	6 (2.1)	17 (5.9)	0	44 (15.5)	6 (2.1)	18 (6.3)	0
Mucosal inflammation	40 (14.1)	4 (1.4)	1 (0.3)	0	40 (14.1)	4 (1.4)	1 (0.3)	0
Rash maculo-papular	40 (14.1)	25 (8.8)	4 (1.4)	0	40 (14.1)	25 (8.8)	4 (1.4)	0
Pruritus	38 (13.4)	2 (0.7)	8 (2.8)	0	37 (13.0)	2 (0.7)	9 (3.1)	0
Alopecia	35 (12.3)	0	3 (1.0)	0	36 (12.7)	0	3 (1.0)	0
Dysgeusia	42 (14.8)	0	8 (2.8)	0	35 (12.3)	0	7 (2.4)	0
Dry skin	31 (10.9)	0	4 (1.4)	0	31 (10.9)	0	4 (1.4)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-1.2su, [SCS Appendix 5-Table 14.3.1-1.2]

Adverse events of special interest

Table 63. Overview of AESI by maximum grade - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off				Safety update 2: 30-Sep-2019 cut-off			
	Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287		Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287	
AESI	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
GI toxicity (nausea, vomiting, diarrhea)	216 (76.1)	26 (9.2)	101 (35.2)	4 (1.4)	219 (77.1)	27 (9.5)	101 (35.2)	4 (1.4)
Hyperglycaemia	188 (66.2)	109 (38.4)	30 (10.5)	3 (1.0)	190 (66.9)	109 (38.4)	29 (10.1)	3 (1.0)
Rash	153 (53.9)	57 (20.1)	26 (9.1)	1 (0.3)	153 (53.9)	57 (20.1)	27 (9.4)	1 (0.3)
Hypersensitivity and anaphylactic reactions	46 (16.2)	6 (2.1)	14 (4.9)	1 (0.3)	46 (16.2)	6 (2.1)	15 (5.2)	1 (0.3)
Pancreatitis	22 (7.7)	18 (6.3)	18 (6.3)	15 (5.2)	23 (8.1)	18 (6.3)	18 (6.3)	15 (5.2)
Osteonecrosis of jaw*	-	-	-	-	16 (5.6)	5 (1.8)	5 (1.7)	3 (1.0)
Pneumonitis	5 (1.8)	1 (0.4)	1 (0.3)	1 (0.3)	5 (1.8)	1 (0.4)	1 (0.3)	1 (0.3)
Severe cutaneous reactions	4 (1.4)	3 (1.1)	0	0	4 (1.4)	3 (1.1)	0	0

Numbers (n) represent counts of subjects.
* Osteonecrosis of jaw was added as an AESI in Safety update 2.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03)
Source: Safety update 1-Table 3-10, [SCS Appendix 5-Table 14.3.1-3.1 to Table 14.3.1-3.8].

GI toxicity

Table 64. GI toxicity (nausea, vomiting, diarrhoea) AESI - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)
Number of subjects with at least one event	216 (76.1) (70.7 - 80.9)	101 (35.2) (29.7 - 41.0)	219 (77.1) (71.8 - 81.9)	101 (35.2) (29.7 - 41.0)
Maximum grade				
Grade 2 AEs	75 (26.4)	31 (10.8)	78 (27.5)	31 (10.8)
Grade 3 AEs	26 (9.2)	4 (1.4)	27 (9.5)	4 (1.4)
Treatment-related AEs	168 (59.2)	59 (20.6)	172 (60.6)	58 (20.2)
SAEs	12 (4.2)	4 (1.4)	12 (4.2)	4 (1.4)
Action taken				
Permanently discontinued	13 (4.6)	0	14 (4.9)	0
Dose adjusted	21 (7.4)	1 (0.3)	21 (7.4)	1 (0.3)
Temporarily interrupted	44 (15.5)	8 (2.8)	43 (15.1)	8 (2.8)
None/NA/Unknown	205 (72.2)	98 (34.1)	208 (73.2)	98 (34.1)
Medication or therapy taken	130 (45.8)	40 (13.9)	131 (46.1)	40 (13.9)
AE outcome				
Recovered/resolved	207 (72.9)	96 (33.4)	208 (73.2)	96 (33.4)
Recovering/resolving	8 (2.8)	1 (0.3)	10 (3.5)	1 (0.3)
Not recovered/not resolved	30 (10.6)	12 (4.2)	32 (11.3)	11 (3.8)
Recovered/resolved with sequelae	1 (0.4)	0	2 (0.7)	0
Missing	2 (0.7)	1 (0.3)	3 (1.1)	1 (0.3)

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken and for outcome.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-3.4su, [SCS Appendix 5-Table 14.3.1-3.4]

Diarrhoea, nausea and vomiting were reported in 59.5%, 46.8% and 28.5% of the patients, respectively. Grade 2 and 3 diarrhoea events were reported in 19.7% and 7.0% of patients, respectively, with a median time to onset of grade ≥2 diarrhoea of 50 days (range: 1 day to 954 days).

59.5% of patients (n=169) experienced diarrhoea during treatment with Piqray. Grade 3 diarrhoea occurred in 7% (n=20) of patients with no reported cases of grade 4. Among patients with grade 2 or 3 diarrhoea (n=76), the median time to onset was 50 days (range: 1 to 954 days).

Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with Piqray and resolved with appropriate intervention. Antiemetics (e.g. ondansetron) and antidiarrhoeal medicinal products (e.g. loperamide) were used in 28/153 (17.6%) and 109/169 (64.5%) patients, respectively, to manage symptoms.

Dose reductions of Piqray were required in 5.6% of patients and 2.8% of patients discontinued Piqray due to diarrhoea. In the 169 patients who experienced diarrhoea, antidiarrhoeal medications (e.g. loperamide) were required to manage symptoms in 64.5% (109/169).

Hyperglycaemia

Hyperglycaemia (FPG >160 mg/dl) was reported in 190 (66.9%) patients; grade 2 (FPG 160-250 mg/dl), 3 (FPG >250-500 mg/dl) and 4 (FPG >500 mg/dl) events were reported in 16.2%, 33.8% and 3.9% of patients, respectively.

Hyperglycaemia occurred more frequently in patients who were diabetic (0 out of 12 patients [0%] with grade 1-2, and 10 out of 12 patients [83.3%] with grade 3-4), pre-diabetic (42 out of 159 patients [26.4%] with grade 1-2, and 77 out of 159 patients [48.4%] with grade 3-4), had BMI ≥30 at screening (13 out of 74 patients [17.6%] with grade 1-2, and 38 out of 74 patients [51.4%] with grade 3-4) or ≥75 years of age (6 out of 34 patients [17.6%] with grade 1-2, and 19 out of 34 patients [55.9%] with grade 3-4).

Based on baseline FPG and HbA1c values, 56% of patients were considered pre-diabetic (FPG >100-126 mg/dl [5.6 to 6.9 mmol/l] and/or HbA1c 5.7-6.4%) and 4.2% of patients were considered diabetic (FPG ≥126 mg/dl [≥7.0 mmol/l] and/or HbA1c ≥6.5%). 74.8% of patients who were pre-diabetic at baseline experienced hyperglycaemia (any grade) when treated with alpelisib. Among all patients with hyperglycaemia of grade ≥2 (FPG ≥160 mg/dl), the median time to first occurrence was 15 days (range: 5 days to 900 days) (based on laboratory findings). The median duration of grade ≥2 hyperglycaemia was 10 days (95% CI: 8 to 13 days). In patients with grade ≥2 hyperglycaemia, median time to improvement (at least one grade from the first event) was 8 days (95% CI: 8 to 10 days). In all patients who continued on fulvestrant after discontinuing Piqray, FPG levels returned to baseline (normal).

Patients with a history of diabetes mellitus intensified use of antidiabetic medicinal products while on treatment with Piqray.

Table 65. Hyperglycaemia AESI - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)
Number of subjects with at least one event	188 (66.2) (60.4 - 71.7)	30 (10.5) (7.2 - 14.6)	190 (66.9) (61.1 - 72.3)	29 (10.1) (6.9 - 14.2)
Maximum grade				
Grade 2 AEs	45 (15.8)	6 (2.1)	46 (16.2)	6 (2.1)
Grade 3 AEs	96 (33.8)	2 (0.7)	96 (33.8)	2 (0.7)
Grade 4 AEs	13 (4.6)	1 (0.3)	13 (4.6)	1 (0.3)
Treatment-related AEs	176 (62.0)	18 (6.3)	178 (62.7)	17 (5.9)
SAEs	30 (10.6)	0	30 (10.6)	0
Action taken				
Permanently discontinued	19 (6.7)	0	20 (7.0)	0
Dose adjusted	83 (29.2)	2 (0.7)	83 (29.2)	2 (0.7)
Temporarily interrupted	75 (26.4)	1 (0.3)	75 (26.4)	1 (0.3)
None/NA/Unknown	167 (58.8)	29 (10.1)	169 (59.5)	28 (9.8)
Medication or therapy taken	164 (57.7)	14 (4.9)	165 (58.1)	13 (4.5)
AE outcome				
Recovered/resolved	167 (58.8)	23 (8.0)	171 (60.2)	23 (8.0)
Recovering/resolving	10 (3.5)	1 (0.3)	9 (3.2)	1 (0.3)
Not recovered/not resolved	34 (12.0)	6 (2.1)	35 (12.3)	5 (1.7)
Recovered/resolved with sequelae	6 (2.1)	1 (0.3)	6 (2.1)	1 (0.3)
Unknown	3 (1.1)	1 (0.3)	3 (1.1)	1 (0.3)
Missing	8 (2.8)	1 (0.3)	3 (1.1)	0

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-3.1su, [SCS Appendix 5-Table 14.3.1-3.1]

In the 190 patients with hyperglycaemia, 87.4% (166/190) were managed with antidiabetic medication, and 75.8% (144/190) reported use of metformin as single agent or in combination with other antidiabetic medication (e.g. insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors and sulfonylureas).

Oral antidiabetic medication was used in 154 patients. Out of these 154 patients, 17 (11.0%) discontinued study treatment due to hyperglycaemia. Concomitant insulin medication was used in 54 patients; of these 13 (24.1%) discontinued study treatment due to hyperglycaemia.

Out of 162 patients with grade ≥2 hyperglycaemia, 155 had at least 1 grade improvement, median time to improvement from the first event was 8 days (95% CI: 8 to 10 days).

Of the patients with elevated FPG who continued fulvestrant treatment after discontinuing Piqray (n=58), 98.3% (n=57) had FPG levels that returned to baseline.

Table 66. Use of anti-diabetic medication – Study C2301 (Safety Set) DCO 30 Sept 2019

Anti-diabetic treatment	Alpelisib 300mg qd + Fulv N=284 n (%)	Placebo qd + Fulv N=287 n (%)
Subjects with anti-diabetic treatment at baseline	17 (6.0)	24 (8.4)
Subjects who did not have anti-diabetic treatment at baseline and started anti-diabetic treatment during the study	153 (53.9)	7 (2.4)
Subjects who did not have anti-diabetic treatment (neither at baseline nor during the study)	114 (40.1)	256 (89.2)

Rash

Rash events (including rash maculopapular, macular, generalised, papular and pruritic, dermatitis and dermatitis acneiform) were reported in 153 (53.9%) patients. Rash was predominantly mild or moderate (grade 1 or 2) and responsive to therapy, and in some cases rash was accompanied by pruritus and dry skin. Grade 2 and 3 events were reported in 13.7% and 20.1% of patients, respectively, with a median time to first onset of 12 days (range: 2 days to 220 days).

Among patients who received prophylactic anti-rash treatment including antihistamines, rash was reported less frequently than in the overall population; 26.1% vs 53.9% for all grades, 11.4% vs 20.1% for grade 3, and 3.4% vs 4.2% for rash leading to the permanent discontinuation of Piqray.

Table 67. Rash AESI - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)
Number of subjects with at least one event	153 (53.9) (47.9 - 59.8)	26 (9.1) (6.0 - 13.0)	153 (53.9) (47.9 - 59.8)	27 (9.4) (6.3 - 13.4)
Maximum grade				
Grade 2 AEs	39 (13.7)	3 (1.0)	39 (13.7)	3 (1.0)
Grade 3 AEs	57 (20.1)	1 (0.3)	57 (20.1)	1 (0.3)
Treatment-related AEs	140 (49.3)	17 (5.9)	139 (48.9)	17 (5.9)
SAEs	10 (3.5)	0	10 (3.5)	0
Action taken				
Permanently discontinued	12 (4.2)	0	12 (4.2)	0
Dose adjusted	26 (9.2)	0	26 (9.2)	0
Temporarily interrupted	62 (21.8)	1 (0.3)	62 (21.8)	1 (0.3)
None/NA/Unknown	123 (43.3)	26 (9.1)	124 (43.7)	27 (9.4)
Medication or therapy taken	127 (44.7)	16 (5.6)	127 (44.7)	16 (5.6)
AE outcome				
Recovered/resolved	144 (50.7)	20 (7.0)	145 (51.1)	21 (7.3)
Recovering/resolving	3 (1.1)	2 (0.7)	4 (1.4)	1 (0.3)
Not recovered/not resolved	14 (4.9)	6 (2.1)	10 (3.5)	7 (2.4)
Recovered/resolved with sequelae	1 (0.4)	0	0	0
Unknown	1 (0.4)	0	2 (0.7)	0

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-3.2su, [SCS Appendix 5-Table 14.3.1-3.2]

Hypersensitivity

Table 68. Hypersensitivity and anaphylactic reactions AESI – Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)
Number of subjects with at least one event	46 (16.2) (12.1 - 21.0)	14 (4.9) (2.7 - 8.0)	46 (16.2) (12.1 - 21.0)	15 (5.2) (3.0 - 8.5)
Maximum grade				
Grade 2 AEs	13 (4.6)	3 (1.0)	13 (4.6)	3 (1.0)
Grade 3 AEs	5 (1.8)	1 (0.3)	5 (1.8)	1 (0.3)
Grade 4 AEs	1 (0.4)	0	1 (0.4)	0
Treatment-related AEs	20 (7.0)	6 (2.1)	23 (8.1)	6 (2.1)
SAEs	6 (2.1)	0	6 (2.1)	0
Action taken				
Permanently discontinued	4 (1.4)	0	4 (1.4)	0
Dose adjusted	2 (0.7)	0	2 (0.7)	0
Temporarily interrupted	5 (1.8)	0	6 (2.1)	0
None/NA/Unknown	38 (13.4)	14 (4.9)	39 (13.7)	15 (5.2)
Medication or therapy taken	29 (10.2)	6 (2.1)	29 (10.2)	6 (2.1)
AE outcome				
Recovered/resolved	39 (13.7)	9 (3.1)	40 (14.1)	11 (3.8)
Not recovered/not resolved	6 (2.1)	4 (1.4)	7 (2.5)	4 (1.4)
Recovered/resolved with sequelae	1 (0.4)	1 (0.3)	1 (0.4)	0
Unknown	1 (0.4)	0	0	0
Missing	1 (0.4)	0	2 (0.7)	0

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-3.6su, [SCS Appendix 5-Table 14.3.1-3.6]

Pancreatitis

Table 69. Pancreatitis - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284	Placebo plus fulvestrant N=287	Alpelisib 300 mg plus fulvestrant N=284	Placebo plus fulvestrant N=287
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Number of subjects with at least one event	22 (7.7) (4.9 - 11.5)	18 (6.3) (3.8 - 9.7)	23 (8.1) (5.2 - 11.9)	18 (6.3) (3.8 - 9.7)
Maximum grade				
Grade 2 AEs	2 (0.7)	0	2 (0.7)	0
Grade 3 AEs	15 (5.3)	12 (4.2)	14 (4.9)	12 (4.2)
Grade 4 AEs	3 (1.1)	3 (1.0)	4 (1.4)	3 (1.0)
Treatment-related AEs	14 (4.9)	12 (4.2)	15 (5.3)	12 (4.2)
SAEs	2 (0.7)	0	2 (0.7)	0
Action taken				
Permanently discontinued	4 (1.4)	4 (1.4)	4 (1.4)	6 (2.1)
Dose adjusted	5 (1.8)	2 (0.7)	5 (1.8)	2 (0.7)
Temporarily interrupted	9 (3.2)	10 (3.5)	9 (3.2)	11 (3.8)
None/NA/Unknown	15 (5.3)	14 (4.9)	16 (5.6)	14 (4.9)
Medication or therapy taken	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)
AE outcome				
Recovered/resolved	18 (6.3)	16 (5.6)	20 (7.0)	16 (5.6)
Recovering/resolving	3 (1.1)	3 (1.0)	2 (0.7)	3 (1.0)
Not recovered/not resolved	4 (1.4)	3 (1.0)	5 (1.8)	2 (0.7)
Missing	1 (0.4)	1 (0.3)	0	1 (0.3)

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-3.5su, [SCS Appendix 5-Table 14.3.1-3.5]

Pneumonitis

Table 70. Pneumonitis AESI - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284	Placebo plus fulvestrant N=287	Alpelisib 300 mg plus fulvestrant N=284	Placebo plus fulvestrant N=287
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Number of subjects with at least one event	5 (1.8) (0.6 - 4.1)	1 (0.3) (0.0 - 1.9)	5 (1.8) (0.6 - 4.1)	1 (0.3) (0.0 - 1.9)
Maximum grade				
Grade 2 AEs	3 (1.1)	0	3 (1.1)	0
Grade 3 AEs	1 (0.4)	1 (0.3)	1 (0.4)	1 (0.3)
Treatment-related AEs	4 (1.4)	1 (0.3)	4 (1.4)	1 (0.3)
SAEs	3 (1.1)	1 (0.3)	3 (1.1)	1 (0.3)
Action taken				
Permanently discontinued	4 (1.4)	1 (0.3)	4 (1.4)	1 (0.3)
None/NA/Unknown	1 (0.4)	0	1 (0.4)	0
Medication or therapy taken	4 (1.4)	1 (0.3)	4 (1.4)	1 (0.3)
AE outcome				
Recovered/resolved	5 (1.8)	0	5 (1.8)	0
Not recovered/not resolved	0	1 (0.3)	0	1 (0.3)

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-14.3.1-3.3su, [SCS Appendix 5-Table 14.3.1-3.3]

Severe cutaneous reactions

Table 71: Severe cutaneous reactions AESI - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)
Number of subjects with at least one event	4 (1.4) (0.4 - 3.6)	0 (0.0 - 1.3)	4 (1.4) (0.4 - 3.6)	0 (0.0 - 1.3)
Maximum grade				
Grade 2 AEs	1 (0.4)	0	1 (0.4)	0
Grade 3 AEs	3 (1.1)	0	3 (1.1)	0
Treatment-related AEs	4 (1.4)	0	4 (1.4)	0
SAEs	4 (1.4)	0	4 (1.4)	0
Action taken				
Permanently discontinued	3 (1.1)	0	3 (1.1)	0
Dose adjusted	2 (0.7)	0	2 (0.7)	0
Temporarily interrupted	2 (0.7)	0	2 (0.7)	0
None/NA/Unknown	2 (0.7)	0	2 (0.7)	0
Medication or therapy taken	4 (1.4)	0	4 (1.4)	0
AE outcome				
Recovered/resolved	4 (1.4)	0	4 (1.4)	0

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-3.7su, [SCS Appendix 5-Table 14.3.1-3.7]

Osteonecrosis of the jaw

ONJ was reported in 5.6% patients (16/284) in the Piqray plus fulvestrant arm. Fifteen patients experiencing ONJ were exposed to concomitant bisphosphonates (e.g. zoledronic acid).

Table 72: Osteonecrosis of jaw AESI - Study C2301 (Safety set)

	Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%) (95% CI)	Placebo plus fulvestrant N=287 n (%) (95% CI)
Number of subjects with at least one event	16 (5.6) (3.3 - 9.0)	5 (1.7) (0.6 - 4.0)
Maximum grade		
Grade 2 AEs	10 (3.5)	2 (0.7)
Grade 3 AEs	5 (1.8)	3 (1.0)
Treatment-related AEs	2 (0.7)	0
SAEs	8 (2.8)	2 (0.7)
Action taken		
Dose adjusted	1 (0.4)	0
Temporarily interrupted	4 (1.4)	1 (0.3)
None/NA/Unknown	15 (5.3)	4 (1.4)
Medication or therapy taken	14 (4.9)	5 (1.7)
AE outcome		
Recovered/resolved	8 (2.8)	3 (1.0)
Recovering/resolving	2 (0.7)	0
Not recovered/not resolved	7 (2.5)	2 (0.7)
Missing	1 (0.4)	0

Numbers (n) represent counts of subjects. Action taken refers to alpelisib/placebo and/or fulvestrant. A subject may be counted in several rows for action taken.
MedDRA version 22.1; CTCAE version 4.03.
Source: [SCS Appendix 5-Table 14.3.1-3.8]

Adverse drug reactions (ADRs)

ADRs from the phase III clinical study and post-marketing experience are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 73. Adverse drug reactions of alpelisib in Study C2301

Adverse drug reaction	Any grade (%)		Grade 3 or 4 (%)
Infections and infestations			
Urinary tract infection[1]	Very common	29 (10.2)	2 (0.7)*
Blood and lymphatic system disorders			
Anaemia	Very common	125 (44.0)	14 (4.9)*
Lymphocyte count decreased	Very common	157 (55.3)	26 (9.2)
Platelet count decreased	Very common	43 (15.1)	4 (1.4)*
Immune system disorders			
Hypersensitivity[2]	Common	11 (3.9)	2 (0.7)*
Metabolism and nutrition disorders			
Glucose plasma increased	Very common	225 (79.2)	111 (39.1)
Glucose plasma decreased	Very common	76 (26.8)	1 (0.4)
Decreased appetite	Very common	102 (35.9)	2 (0.7)*
Hypokalaemia	Very common	42 (14.8)	18 (6.3)
Hypocalcaemia	Very common	79 (27.8)	6 (2.1)
Magnesium decreased	Very common	34 (12.0)	1 (0.4)
Dehydration	Common	10 (3.5)	1 (0.4)*
Ketoacidosis[3]	Uncommon	2 (0.7)	2 (0.7)
Psychiatric disorders			
Insomnia	Common	22 (7.7)	
Nervous system disorders			
Headache	Very common	55 (19.4)	2 (0.7)*
Dysgeusia[4]	Very common	44 (15.5)	1 (0.4)*
Eye disorders			
Vision blurred	Common	15 (5.3)	1 (0.4)*
Dry eye	Common	10 (3.5)	
Vascular disorders			
Hypertension	Common	27 (9.5)	13 (4.6)
Lymphoedema	Common	16 (5.6)	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis[5]	Common	5 (1.8)	1 (0.4)*
Gastrointestinal disorders			
Diarrhoea	Very common	169 (59.5)	20 (7.0)*
Nausea	Very common	133 (46.8)	8 (2.8)*
Stomatitis[6]	Very common	86 (30.3)	7 (2.5)*
Vomiting	Very common	81 (28.5)	2 (0.7)*
Abdominal pain	Very common	50 (17.6)	4 (1.4)*
Dyspepsia	Very common	33 (11.6)	
Toothache	Common	13 (4.6)	1 (0.4)*
Gingivitis	Common	11 (3.9)	1 (0.4)*
Gingival pain	Common	9 (3.2)	
Cheilitis	Common	8 (2.8)	
Pancreatitis	Uncommon	1 (0.4)	1 (0.4)

Skin and subcutaneous tissue disorders			
Rash[7]	Very common	147 (51.8)	55 (19.4)*
Alopecia	Very common	58 (20.4)	
Pruritus	Very common	53 (18.7)	2 (0.7)*
Dry skin[8]	Very common	53 (18.7)	1 (0.4)*
Erythema[9]	Common	18 (6.3)	2 (0.7)*
Dermatitis[10]	Common	10 (3.5)	2 (0.7)*
Palmar-plantar erythrodysaesthesia syndrome	Common	5 (1.8)	
Erythema multiforme	Common	3 (1.1)	2 (0.7)*
Stevens-Johnson syndrome	Uncommon	1 (0.4)	1 (0.4)*
Drug reaction with eosinophilia and systemic symptoms (DRESS)[#]	Not known	Not known	Not known
Musculoskeletal and connective tissue disorders			
Muscle spasms	Common	22 (7.7)	
Myalgia	Common	19 (6.7)	1 (0.4)*
Osteonecrosis of jaw	Common	16 (5.6)	5 (1.8)*
Renal and urinary disorders			
Acute kidney injury	Common	16 (5.6)	5 (1.8)
General disorders and administration site conditions			
Fatigue[11]	Very common	123 (43.3)	16 (5.6)*
Mucosal inflammation	Very common	56 (19.7)	6 (2.1)*
Oedema peripheral	Very common	47 (16.5)	
Pyrexia	Very common	45 (15.8)	2 (0.7)
Mucosal dryness[12]	Very common	36 (12.7)	1 (0.4)
Oedema[13]	Common	18 (6.3)	
Investigations			
Weight decreased	Very common	79 (27.8)	15 (5.3)*
Blood creatinine increased	Very common	192 (67.6)	8 (2.8)*
Gamma-glutamyltransferase increased	Very common	151 (53.2)	34 (12.0)
Alanine aminotransferase increased	Very common	125 (44.0)	12 (4.2)*
Lipase increased	Very common	121 (42.6)	20 (7.0)
Activated partial thromboplastin time (aPTT) prolonged	Very common	63 (22.2)	2 (0.7)
Albumin decreased	Very common	41 (14.4)	1 (0.4)
Glycosylated haemoglobin increased	Common	8 (2.8)	0

* No grade 4 ADRs were observed

\# Adverse reactions reported during post-marketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

1 Urinary tract infection: also includes a single case of urosepsis

2 Hypersensitivity: also includes allergic dermatitis

3 Ketoacidosis: also includes diabetic ketoacidosis

4 Dysgeusia: also includes ageusia, hypogeusia

5 Pneumonitis: also includes interstitial lung disease

6 Stomatitis: also includes aphthous ulcer and mouth ulceration

7 Rash: also includes rash maculopapular, rash macular, rash generalised, rash papular, rash pruritic

8 Dry skin: also includes skin fissures, xerosis, xeroderma

9 Erythema: also includes erythema generalised

10 Dermatitis: also includes dermatitis acneiform

11 Fatigue: also includes asthenia

12 Mucosal dryness: also includes dry mouth, vulvovaginal dryness

13 Oedema: also includes face swelling, face oedema, eyelid oedema

Serious adverse events and deaths

Table 74. Overview of deaths and other serious or clinically significant adverse events – Studies C2301 (data cut-off 12 June 2018), X2101 and X1101 (Safety set)

	Study C2301		Study X2101	Study X2101	Study X1101
	Alpelisib plus fulvestrant	Placebo plus fulvestrant	Alpelisib plus fulvestrant	Alpelisib	Alpelisib
	N = 284	N = 287	N = 87	N = 134	N = 33
Category	n (%)	n (%)	n (%)	n (%)	n (%)
All deaths	**78 (27.5)**	**91 (31.7)**	**7 (8.0)**	**15 (11.1)**	**3 (9.1)**
Death within 28/30 days of treatment discontinuation [a]	**7 (2.5)**	**12 (4.2)**	**5 (5.7)**	**13 (9.7)**	**3 (9.1)**
Progressive disease	**5 (1.8)**	**8 (2.8)**	**4 (4.6)**	**12 (9.0)**	**2 (6.1)**
Adverse events	**2 (0.7)**	**4 (1.4)**	**1 (1.1)**	**1 (0.7)**	**1 (3.0)**
Cardio-respiratory arrest	1 (0.4)	0	0	0	0
Second primary malignancy	1 (0.4)	0	0	0	0
Death	0	1 (0.3)	1 (1.1)	0	0
Gastrointestinal haemorrhage	0	1 (0.3)	0	0	0
Pneumonia	0	1 (0.3)	0	0	0
Septic shock	0	1 (0.3)	0	0	0
Tumor embolism	0	0	0	0	1 (3.0)
Hypoxia	0	0	0	1 (0.7)	0
Serious adverse events (SAEs)	**99 (34.9)**	**48 (16.7)**	**29 (33.3)**	**62 (46.3)**	**19 (57.6)**
Suspected to be drug related	64 (22.5)	5 (1.7)	6 (6.9)	4 (3.0)	9 (27.3)
AEs leading to discontinuation	**71 (25.0)**	**13 (4.5)**	**9 (10.3)**	**18 (13.4)**	**9 (27.3)**

AE adverse event

[a] 28 days was used for Studies X2101 and X1101 while 30 days was used for Study C2301

Deaths

In the pivotal study, 78 patients (27.5%) in the alpelisib arm and 91 patients (31.7%) in the placebo arm died in total (cut-off date 12 Jun 2018), and of the 78 deaths in the alpelisib arm, 74 were due to progression of the underlying disease. The remaining four deaths were due to thrombotic microangiopathy, sepsis, cardio-respiratory arrest, and second primary malignancy. Overall, there were more deaths in the placebo arm of the pivotal study and 4 deaths were not due to progression of the underlying disease. Despite the death due to thrombotic microangiopathy could have been related to treatment, it occurred 25 days after the last dose of study treatment at a time of disease progression and the risk of the event was also influenced by concomitant medication. The death due to sepsis is not considered to be related to treatment as it occurred 10 months after the last dose of study treatment. The two remaining deaths from cardio-respiratory arrest and second primary malignancy are also not considered to be treatment-related. No deaths in the placebo arm were treatment-related. Overall, the 3 patients who died from fatal SAEs in the pivotal study were not treatment-related. There were no treatment-related deaths in the phase 1 study.

In a safety update (cut-off date 20 Oct 2018), the total number of deaths increased to 96 (33.8%) in the alpelisib plus fulvestrant group, and 101 (35.2%) in the placebo plus fulvestrant group. Of the 18 additional post-treatment deaths in the alpelisib plus fulvestrant group, 16 deaths were due to breast cancer / disease progression. The two remaining additional post-treatment deaths were due to septic shock and unknown cause. Both deaths occurred more than a year after the last dose of study drug.

In a second safety update (cut-off date 30 Sep 2019), the total number of deaths (i.e. including those that occurred more than 30 days after the last dose of study drug) was 128 (45.1%) in the alpelisib plus fulvestrant group, and 142 (49.5%) in the placebo plus fulvestrant group. Most of these deaths were due to the study indication (119 (41.9%) in the alpelisib plus fulvestrant group, and 128 (44.6%) in the placebo plus fulvestrant group).

Table 75. On-treatment deaths – Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n (%)	Placebo plus fulvestrant N=287 n (%)	Alpelisib 300 mg plus fulvestrant N=284 n (%)	Placebo plus fulvestrant N=287 n (%)
Number of subjects who died	**7 (2.5)**	**12 (4.2)**	**9 (3.2)**	**12 (4.2)**
Primary reason: Study indication	5 (1.8)	9 (3.1)	7 (2.5)	9 (3.1)
Primary reason: Other	2 (0.7)	3 (1.0)	2 (0.7)	3 (1.0)
Cardio-respiratory arrest	1 (0.4)	0	1 (0.4)	0
Gastrointestinal haemorrhage	0	1 (0.3)	0	1 (0.3)
Pneumonia	0	1 (0.3)	0	1 (0.3)
Second primary malignancy	1 (0.4)	0	1 (0.4)	0
Septic shock	0	1 (0.3)	0	1 (0.3)

Numbers (n) represent counts of subjects.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2).
Source: SCS Appendix 3-Table 14.3.1-1.3su, [SCS Appendix 5-Table 14.3.1-1.3]

Among the 87 patients treated with alpelisib plus fulvestrant in the supportive phase 1 study X2101, a total of seven deaths were reported; five of these deaths occurred on treatment (i.e. within 28 days after the end of study treatment). All deaths occurred in the alpelisib 400 mg plus fulvestrant dose group. Of the five on-treatment deaths, four deaths were due progression of the underlying disease. One patient died of an unknown cause, nine days after a CT scan revealed progressive disease. None of these deaths were suspected to be related to the alpelisib plus fulvestrant combination treatment.

Serious adverse events

Table 76. Serious adverse events (at least 1% in either treatment group) by preferred term and maximum grade –Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off				Safety update 2: 30-Sep-2019 cut-off			
	Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287		Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	100 (35.2)	82 (28.9)	49 (17.1)	44 (15.3)	104 (36.6)	85 (29.9)	54 (18.8)	48 (16.7)
Hyperglycaemia	28 (9.9)	25 (8.8)	0	0	28 (9.9)	25 (8.8)	0	0
Diarrhoea	8 (2.8)	4 (1.4)	0	0	8 (2.8)	4 (1.4)	0	0
Osteonecrosis of jaw	6 (2.1)	4 (1.4)	1 (0.3)	1 (0.3)	8 (2.8)	5 (1.8)	2 (0.7)	2 (0.7)
Abdominal pain	6 (2.1)	4 (1.4)	2 (0.7)	1 (0.3)	6 (2.1)	4 (1.4)	2 (0.7)	1 (0.3)
Acute kidney injury	5 (1.8)	3 (1.1)	1 (0.3)	1 (0.3)	5 (1.8)	3 (1.1)	1 (0.3)	1 (0.3)
Anaemia	5 (1.8)	3 (1.1)	0	0	5 (1.8)	3 (1.1)	0	0
Nausea	5 (1.8)	4 (1.4)	2 (0.7)	1 (0.3)	5 (1.8)	4 (1.4)	2 (0.7)	1 (0.3)
Rash	4 (1.4)	3 (1.1)	0	0	5 (1.8)	4 (1.4)	0	0
Vomiting	5 (1.8)	2 (0.7)	3 (1.0)	1 (0.3)	5 (1.8)	2 (0.7)	3 (1.0)	1 (0.3)
Dyspnoea	2 (0.7)	1 (0.4)	4 (1.4)	4 (1.4)	4 (1.4)	3 (1.1)	4 (1.4)	4 (1.4)
Pleural effusion	3 (1.1)	3 (1.1)	5 (1.7)	4 (1.4)	4 (1.4)	4 (1.4)	5 (1.7)	4 (1.4)
Pyrexia	4 (1.4)	0	0	0	4 (1.4)	0	0	0
Stomatitis	4 (1.4)	2 (0.7)	0	0	4 (1.4)	2 (0.7)	0	0
Dehydration	3 (1.1)	1 (0.4)	3 (1.0)	3 (1.0)	3 (1.1)	1 (0.4)	3 (1.0)	3 (1.0)
Erythema multiforme	3 (1.1)	2 (0.7)	0	0	3 (1.1)	2 (0.7)	0	0
Hypersensitivity	3 (1.1)	1 (0.4)	0	0	3 (1.1)	1 (0.4)	0	0
Hypokalaemia	3 (1.1)	3 (1.1)	1 (0.3)	0	3 (1.1)	3 (1.1)	1 (0.3)	0
Mucosal inflammation	3 (1.1)	3 (1.1)	0	0	3 (1.1)	3 (1.1)	0	0
Pneumonia	3 (1.1)	3 (1.1)	5 (1.7)	5 (1.7)	3 (1.1)	3 (1.1)	6 (2.1)	5 (1.7)
Pulmonary embolism	2 (0.7)	2 (0.7)	3 (1.0)	2 (0.7)	3 (1.1)	3 (1.1)	3 (1.0)	2 (0.7)
Rash maculo-papular	3 (1.1)	2 (0.7)	0	0	3 (1.1)	2 (0.7)	0	0
Urinary tract infection	2 (0.7)	1 (0.4)	3 (1.0)	3 (1.0)	2 (0.7)	1 (0.4)	3 (1.0)	3 (1.0)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-1.6su, [SCS Appendix 5-Table 14.3.1-1.6]

Laboratory findings

Haematology

Table 77. Worst post-baseline haematology abnormalities by maximum grade - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off						Safety update 2: 30-Sep-2019 cut-off					
	Alpelisib 300 mg plus fulvestrant N=284			Placebo plus fulvestrant N=287			Alpelisib 300 mg plus fulvestrant N=284			Placebo plus fulvestrant N=287		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hemoglobin (Hyper)	15 (5.3)	1 (0.4)	0	3 (1.0)	0	0	15 (5.3)	1 (0.4)	0	3 (1.0)	0	0
Hemoglobin (Hypo)	119 (41.9)	13 (4.6)	0	83 (28.9)	3 (1.0)	0	125 (44.0)	14 (4.9)	0	87 (30.3)	4 (1.4)	0
Leukocytes (Hyper)	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
Leukocytes (Hypo)	77 (27.1)	3 (1.1)	1 (0.4)	88 (30.7)	0	1 (0.3)	80 (28.2)	3 (1.1)	1 (0.4)	91 (31.7)	0	1 (0.3)
Lymphocytes (Hyper)	13 (4.6)	2 (0.7)	0	8 (2.8)	2 (0.7)	0	13 (4.6)	2 (0.7)	0	8 (2.8)	2 (0.7)	0
Lymphocytes (Hypo)	152 (53.5)	20 (7.0)	3 (1.1)	116 (40.4)	14 (4.9)	0	157 (55.3)	23 (8.1)	3 (1.1)	118 (41.1)	14 (4.9)	0
Neutrophils (Hypo)	55 (19.4)	7 (2.5)	2 (0.7)	66 (23.0)	4 (1.4)	2 (0.7)	57 (20.1)	7 (2.5)	2 (0.7)	70 (24.4)	4 (1.4)	2 (0.7)
Platelets (Hypo)	41 (14.4)	2 (0.7)	2 (0.7)	18 (6.3)	1 (0.3)	1 (0.3)	43 (15.1)	2 (0.7)	2 (0.7)	19 (6.6)	2 (0.7)	1 (0.3)
INR (Hyper)	46 (16.2)	0	0	48 (16.7)	1 (0.3)	0	50 (17.6)	0	0	51 (17.8)	2 (0.7)	0
aPTT (Hyper)	61 (21.5)	2 (0.7)	0	46 (16.0)	2 (0.7)	0	63 (22.2)	2 (0.7)	0	52 (18.1)	2 (0.7)	0

Baseline is defined as the last non-missing value prior to the start date of study treatment.
Percentage is based on N.
Subjects are counted only for the worst grade observed post-baseline.
Laboratory assessments performed more than 30 days after last study treatment administration date are not summarized.
Source: SCS Appendix 3-Table 14.3-3.1su, [SCS Appendix 5-Table 14.3-3.1]

Clinical chemistry

Table 78. Worst post-baseline chemistry abnormalities by maximum grade - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off						Safety update 2: 30-Sep-2019 cut-off					
	Alpelisib 300 mg plus fulvestrant N=284			Placebo plus fulvestrant N=287			Alpelisib 300 mg plus fulvestrant N=284			Placebo plus fulvestrant N=287		
Parameter	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
ALT (Hyper)	125 (44.0)	8 (2.8)	2 (0.7)	100 (34.8)	7 (2.4)	0	125 (44.0)	9 (3.2)	3 (1.1)	101 (35.2)	7 (2.4)	0
Albumin (Hypo)	39 (13.7)	0	0	22 (7.7)	0	0	41 (14.4)	1 (0.4)	0	22 (7.7)	0	0
Alkaline phosphatase (Hyper)	106 (37.3)	2 (0.7)	0	129 (44.9)	6 (2.1)	0	110 (38.7)	2 (0.7)	0	132 (46.0)	6 (2.1)	0
Amylase (Hyper)	31 (10.9)	5 (1.8)	1 (0.4)	32 (11.1)	6 (2.1)	0	32 (11.3)	6 (2.1)	1 (0.4)	33 (11.5)	6 (2.1)	0
AST (Hyper)	139 (48.9)	6 (2.1)	2 (0.7)	140 (48.8)	5 (1.7)	2 (0.7)	143 (50.4)	7 (2.5)	3 (1.1)	141 (49.1)	6 (2.1)	2 (0.7)
Bilirubin (Hyper)	17 (6.0)	0	0	12 (4.2)	3 (1.0)	0	18 (6.3)	0	0	12 (4.2)	3 (1.0)	0
Calcium (Hyper)	21 (7.4)	0	1 (0.4)	23 (8.0)	1 (0.3)	1 (0.3)	22 (7.7)	1 (0.4)	1 (0.4)	25 (8.7)	1 (0.3)	1 (0.3)
Calcium (Hypo)	79 (27.8)	5 (1.8)	1 (0.4)	57 (19.9)	1 (0.3)	3 (1.0)	79 (27.8)	5 (1.8)	1 (0.4)	57 (19.9)	2 (0.7)	3 (1.0)
Cholesterol (Hyper)	91 (32.0)	0	0	119 (41.5)	0	1 (0.3)	98 (34.5)	0	0	127 (44.3)	0	1 (0.3)
Creatine kinase (Hyper)	51 (18.0)	2 (0.7)	0	46 (16.0)	2 (0.7)	0	57 (20.1)	2 (0.7)	0	48 (16.7)	2 (0.7)	0
Creatinine (Hyper)	191 (67.3)	8 (2.8)	0	73 (25.4)	2 (0.7)	0	192 (67.6)	8 (2.8)	0	75 (26.1)	2 (0.7)	0
Creatinine clearance (Hypo)	4 (1.4)	0	0	2 (0.7)	0	0	5 (1.8)	0	0	2 (0.7)	0	0
GGT (Hyper)	149 (52.5)	28 (9.9)	3 (1.1)	131 (45.6)	24 (8.4)	5 (1.7)	151 (53.2)	30 (10.6)	4 (1.4)	133 (46.3)	27 (9.4)	5 (1.7)
Glucose (Hyper)	224 (78.9)	95 (33.5)	16 (5.6)	100 (34.8)	3 (1.0)	1 (0.3)	225 (79.2)	95 (33.5)	16 (5.6)	100 (34.8)	3 (1.0)	2 (0.7)
Glucose (Hypo)	76 (26.8)	0	1 (0.4)	40 (13.9)	0	0	76 (26.8)	0	1 (0.4)	40 (13.9)	0	0
Lipase (Hyper)	122 (43.0)	18 (6.3)	3 (1.1)	74 (25.8)	14 (4.9)	4 (1.4)	121 (42.6)	16 (5.6)	4 (1.4)	75 (26.1)	14 (4.9)	4 (1.4)
Magnesium (Hyper)	19 (6.7)	2 (0.7)	0	7 (2.4)	0	0	22 (7.7)	3 (1.1)	0	14 (4.9)	1 (0.3)	0
Magnesium (Hypo)	31 (10.9)	1 (0.4)	0	12 (4.2)	0	0	34 (12.0)	1 (0.4)	0	13 (4.5)	0	0
Potassium (Hyper)	49 (17.3)	7 (2.5)	0	67 (23.3)	12 (4.2)	0	53 (18.7)	7 (2.5)	1 (0.4)	69 (24.0)	13 (4.5)	1 (0.3)
Potassium (Hypo)	40 (14.1)	13 (4.6)	3 (1.1)	8 (2.8)	2 (0.7)	0	42 (14.8)	14 (4.9)	4 (1.4)	8 (2.8)	2 (0.7)	0
Sodium (Hyper)	29 (10.2)	2 (0.7)	0	21 (7.3)	1 (0.3)	0	32 (11.3)	2 (0.7)	0	22 (7.7)	1 (0.3)	0
Sodium (Hypo)	39 (13.7)	11 (3.9)	2 (0.7)	33 (11.5)	9 (3.1)	0	41 (14.4)	11 (3.9)	2 (0.7)	33 (11.5)	9 (3.1)	0
Triglycerides (Hyper)	56 (19.7)	1 (0.4)	0	54 (18.8)	1 (0.3)	0	59 (20.8)	1 (0.4)	0	58 (20.2)	1 (0.3)	0
Urate (Hyper)	122 (43.0)	0	9 (3.2)	119 (41.5)	0	5 (1.7)	126 (44.4)	0	9 (3.2)	119 (41.5)	0	5 (1.7)

Baseline is defined as the last non-missing value prior to the start date of study treatment.
Percentage is based on N.
Subjects are counted only for the worst grade observed post-baseline.
Laboratory assessments performed more than 30 days after last study treatment administration date are not summarized.
Source: SCS Appendix 3-Table 14.3-3.2su, [SCS Appendix 5-Table 14.3-3.2x]

More patients had altered clinical chemistry with alpelisib and especially increase of glucose (+44.0%), creatinine (+42.2%), lipase (+16.5%). There was an increased risk also for low glucose (+11.8%) and potassium (+10.9%). High-grade events of hyperglycaemia were common (+32.8%) (see section of AESI).

Vital signs, physical findings, and other observations related to safety

Weight decreased

The number of patients with a decrease in weight ≥10% from baseline was 42.2% vs 9.3% in the alpelisib arm versus the placebo arm. 3.9% vs 0% of patients had a grade 3 AE and no grade 4 events were reported. Weight

decrease was considered treatment-related in 15.5% vs 1.0% of patients. The body weight of most patients in the pivotal study was in the normal to obese range based on their BMI (median BMI was 26.4 kg/m^2).

ECG

Table 79. Notable ECG values - Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off		Safety update 2: 30-Sep-2019 cut-off	
	Alpelisib 300 mg plus fulvestrant N=284 n/m (%)	Placebo plus fulvestrant N=287 n/m (%)	Alpelisib 300 mg plus fulvestrant N=284 n/m (%)	Placebo plus fulvestrant N=287 n/m (%)
QTcF (ms)				
Increase >30 to ≤60 ms	70/271 (25.8)	39/276 (14.1)	71/271 (26.2)	41/276 (14.9)
Increase >60 ms	15/271 (5.5)	6/276 (2.2)	17/271 (6.3)	7/276 (2.5)
New >450 to ≤480 ms	50/250 (20.0)	35/256 (13.7)	50/250 (20.0)	36/256 (14.1)
New >480 to ≤500 ms	8/269 (3.0)	5/272 (1.8)	9/269 (3.3)	6/272 (2.2)
New >500 ms	3/271 (1.1)	1/275 (0.4)	4/271 (1.5)	1/275 (0.4)
QT (ms)				
Increase >30 to ≤60 ms	102/271 (37.6)	77/276 (27.9)	104/271 (38.4)	79/276 (28.6)
Increase >60 ms	27/271 (10.0)	15/276 (5.4)	28/271 (10.3)	18/276 (6.5)
New >450 to ≤480 ms	30/263 (11.4)	19/268 (7.1)	30/263 (11.4)	23/268 (8.6)
New >480 to ≤500 ms	3/270 (1.1)	3/275 (1.1)	3/270 (1.1)	4/275 (1.5)
New >500 ms	2/271 (0.7)	0/276 (0.0)	3/271 (1.1)	1/276 (0.4)
PR (ms)				
Increase >25% and PR >200 ms	6/248 (2.4)	7/262 (2.7)	6/248 (2.4)	8/262 (3.1)
New PR >200 ms	12/251 (4.8)	16/264 (6.1)	12/251 (4.8)	17/264 (6.4)
QRS (ms)				
Increase >25% and QRS > 120 ms	6/261 (2.3)	2/269 (0.7)	6/261 (2.3)	3/269 (1.1)
New QRS > 120 ms	6/262 (2.3)	5/269 (1.9)	7/262 (2.7)	6/269 (2.2)
HR (bpm)				
Increase >25% and HR >100 bpm	14/265 (5.3)	10/266 (3.8)	17/265 (6.4)	12/266 (4.5)
Decrease >25% and HR <50 bpm	0/272 (0.0)	1/276 (0.4)	0/272 (0.0)	1/276 (0.4)

n: Number of subjects at risk who met the criterion at least once post baseline.
m: Number of subjects at risk.
Source: SCS Appendix 3-Table 14.3-4.2su, [SCS Appendix 5-Table 14.3-4.2]

Safety in special populations

Table 80. Overview of AEs by age group – Study C2301 (Safety set) – DCO 30 September 2019

	Treatment: Alpelisib 300mg qd + Fulv				Treatment: Placebo qd + Fulv			
	< 65 years N=167	65-74 years N=83	75-84 years N=33	85+ years N=1	< 65 years N=153	65-74 years N=95	75-84 years N=35	85+ years N=4
Total AEs	166 (99.4)	82 (98.8)	33 (100)	1 (100)	141 (92.2)	89 (93.7)	33 (94.3)	3 (75.0)
Serious AEs – Total**	51 (30.5)	37 (44.6)	15 (45.5)	1 (100)	24 (15.7)	24 (25.3)	6 (17.1)	0
- Fatal**	0	1 (1.2)	3 (9.1)	0	1 (0.7)	1 (1.1)	2 (5.7)	0
- Hospitalization/prolong existing hospitalization**	51 (30.5)	34 (41.0)	15 (45.5)	1 (100)	24 (15.7)	24 (25.3)	6 (17.1)	0
- Life-threatening**	3 (1.8)	3 (3.6)	4 (12.1)	0	2 (1.3)	2 (2.1)	0	0
- Disability/incapacity**	0	2 (2.4)	1 (3.0)	0	0	2 (2.1)	0	0
- Other (medically significant)**	3 (1.8)	5 (6.0)	1 (3.0)	0	2 (1.3)	1 (1.1)	0	0
AE leading to drop-out [1]	29 (17.4)	32 (38.6)	12 (36.4)	1 (100)	4 (2.6)	8 (8.4)	4 (11.4)	0
Psychiatric disorders [2]	21 (12.6)	20 (24.1)	6 (18.2)	0	18 (11.8)	16 (16.8)	3 (8.6)	1 (25.0)
Nervous system disorders [3]	82 (49.1)	34 (41.0)	13 (39.4)	0	43 (28.1)	29 (30.5)	14 (40.0)	1 (25.0)
Accidents and injuries [4]	10 (6.0)	6 (7.2)	3 (9.1)	0	7 (4.6)	8 (8.4)	3 (8.6)	0
Cardiac disorders [5]	14 (8.4)	4 (4.8)	3 (9.1)	0	11 (7.2)	13 (13.7)	4 (11.4)	1 (25.0)
Vascular disorders [6]	24 (14.4)	21 (25.3)	10 (30.3)	1 (100)	28 (18.3)	14 (14.7)	6 (17.1)	0
Cerebrovascular disorders [7]	1 (0.6)	0	0	0	1 (0.7)	1 (1.1)	1 (2.9)	0
Infections and infestations [8]	76 (45.5)	39 (47.0)	11 (33.3)	0	38 (24.8)	38 (40.0)	15 (42.9)	1 (25.0)
Anticholinergic syndrome [9]	69 (41.3)	34 (41.0)	11 (33.3)	0	35 (22.9)	23 (24.2)	11 (31.4)	1 (25.0)
Quality of life decreased [10]	99 (59.3)	51 (61.4)	19 (57.6)	0	71 (46.4)	46 (48.4)	19 (54.3)	2 (50.0)
Sum of postural hypotension [11]	18 (10.8)	14 (16.9)	7 (21.2)	0	14 (9.2)	10 (10.5)	4 (11.4)	1 (25.0)

**** Source: Novartis Clinical database.**
[1] AEs leading to permanently discontinuation of Alpelisib with or without fulvestrant; [2] AEs in the SOC of psychiatric disorders; [3] AEs in the SOC of nervous system disorders; [4] AEs in the SMQ of accidents and injuries (Narrow); [5] AEs in the SOC of cardiac disorders; [6] AEs in the SOC of vascular disorders; [7] AEs in the SMQ of central nervous system vascular disorders (Narrow); [8] AEs in the SOC of infections and infestations; [9] AEs in the SMQ of anticholinergic syndrome (Narrow); [10] Global quality of life decreased by at least 10% compared to baseline;
[11] AEs with PTs of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, fracture.
Numbers (n) represent counts of subjects.MedDRA version 22.1, CTCAE version 4.03.

In patients ≥65 years of age treated with alpelisib plus fulvestrant, there was a higher incidence of grade 3-4 hyperglycaemia (45.3%) compared to patients <65 years of age (33.5%), while in patients <75 years of age, grade 3-4 hyperglycaemia was 36% compared to 55.9% in patients ≥75 years of age.

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

See PK section.

Discontinuation due to AES

AEs leading to discontinuation were reported in 25.0% of subjects in the alpelisib plus fulvestrant group and 4.5% of subjects in the placebo plus fulvestrant group.

The most frequent ADRs leading to discontinuation in the alpelisib plus fulvestrant group were hyperglycemia (6.3%), rash (4.2%), diarrhoea (2.8%), and fatigue (2.5%).

Table 81. Adverse events leading to discontinuation (at least 0.5% in either treatment group) by preferred term and maximum grade - Study C2301 (Safety set)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 21.0 (original submission) and 21.1 (safety update); CTCAE version 4.03.

	Original MAA DCO date: 12-Jun-2018				90-day Safety Update DCO date: 20-Oct-2018				Interim OS analysis DCO date: 30-Sep-2019			
	Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287		Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287		Alpelisib plus fulvestrant N = 284		Placebo plus fulvestrant N = 287	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	%	%	%	%	%	%	%	%	%	%	%	%
Total	**25.0**	**13.0**	**4.5**	**3.8**	**25.4**	**13.0**	**4.5**	**3.1**	**26.1**	**13.0**	**5.6**	**3.8**
Hyperglycaemia	6.3	4.2	0	0	6.3	4.2	0	0	6.3	4.2	0	0
Rash	3.2	1.1	0	0	3.2	1.1	0	0	3.2	1.1	0	0
Diarrhoea	2.8	0.4	0	0	2.8	0.4	0	0	2.8	0.4	0	0
Fatigue	2.1	1.1	0	0	2.1	1.1	0	0	2.1	1.1	0	0
Nausea	1.8	0.4	0	0	1.8	0.4	0	0	1.8	0.4	0	0
Stomatitis	1.4	0.4	0.3	0	1.4	0.4	0.3	0	1.4	0.4	0.3	0
Decreased appetite	1.4	0	0	0	1.4	0	0	0	1.4	0	0	0
Vomiting	1.1	0	0	0	1.1	0	0	0	1.4	0	0	0
Lipase increased	1.1	0.4	1.4	1.4	1.1	0.4	1.4	1.4	1.1	0.4	1.7	1.4
Hypersensitivity	1.1	0.7	0	0	1.1	0.7	0	0	1.1	0.7	0	0
Pneumonitis	1.1	0.4	0	0	1.1	0.4	0	0	1.1	0.4	0	0
Rash maculo-papular	1.1	0.4	0	0	1.1	0.4	0	0	1.1	0.4	0	0
Erythema	0.7	0.7	0	0	0.7	0.7	0	0	0.7	0.7	0	0
Dry mouth	0.7	0.4	0	0	0.7	0.4	0	0	0.7	0.4	0	0
Mucosal inflammation	0.7	0.4	0	0	0.7	0.4	0	0	0.7	0.4	0	0
Erythema multiforme	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0
Weight decreased	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0
Asthenia	0.4	0	0	0	0.7	0	0	0	0.4	0	0	0
Spinal cord compression	0	0	0.7	0.3	0	0	0.3	0	0	0	0.3	0

Dose reductions and dose interruptions due to AEs

Adverse events requiring dose reduction (alpelisib/placebo) and/or interruption (either alpelisib/placebo or fulvestrant, or both) were reported in 78.5% of subjects in the pelisib plus fulvestrant group compared to 22.6% in the placebo plus fulvestrant group. In the alpelisib plus fulvestrant group dose reductions/dose interruptions were most frequently due to hyperglycaemia (38.4%), diarrhoea (13.7%), and skin-related events (rash [12.7%], rash maculo-papular [10.2%]).

Table 82. Adverse events leading to dose adjustment and/or interruption (at least 1% in either treatment group) by preferred term and maximum grade -Study C2301 (Safety set)

	Safety update 1: 20-Oct-2018 cut-off				Safety update 2: 30-Sep-2019 cut-off			
	Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287		Alpelisib 300 mg plus fulvestrant N=284		Placebo plus fulvestrant N=287	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	224 (78.9)	180 (63.4)	64 (22.3)	40 (13.9)	225 (79.2)	181 (63.7)	66 (23.0)	42 (14.6)
Hyperglycaemia	109 (38.4)	90 (31.7)	2 (0.7)	1 (0.3)	109 (38.4)	90 (31.7)	2 (0.7)	1 (0.3)
Diarrhoea	40 (14.1)	17 (6.0)	4 (1.4)	1 (0.3)	39 (13.7)	17 (6.0)	4 (1.4)	1 (0.3)
Rash	36 (12.7)	25 (8.8)	1 (0.3)	1 (0.3)	38 (13.4)	26 (9.2)	1 (0.3)	1 (0.3)
Rash maculo-papular	29 (10.2)	25 (8.8)	0	0	29 (10.2)	25 (8.8)	0	0
Stomatitis	19 (6.7)	6 (2.1)	0	0	18 (6.3)	6 (2.1)	0	0
Mucosal inflammation	14 (4.9)	4 (1.4)	0	0	14 (4.9)	4 (1.4)	0	0
Nausea	13 (4.6)	4 (1.4)	3 (1.0)	0	13 (4.6)	4 (1.4)	3 (1.0)	0
Lipase increased	11 (3.9)	10 (3.5)	6 (2.1)	5 (1.7)	11 (3.9)	10 (3.5)	7 (2.4)	6 (2.1)
Pyrexia	11 (3.9)	2 (0.7)	2 (0.7)	1 (0.3)	11 (3.9)	2 (0.7)	2 (0.7)	1 (0.3)
Vomiting	10 (3.5)	1 (0.4)	6 (2.1)	1 (0.3)	11 (3.9)	1 (0.4)	6 (2.1)	1 (0.3)
Asthenia	9 (3.2)	3 (1.1)	4 (1.4)	0	10 (3.5)	4 (1.4)	4 (1.4)	0
Fatigue	10 (3.5)	4 (1.4)	2 (0.7)	0	10 (3.5)	4 (1.4)	2 (0.7)	0
Pruritus	10 (3.5)	1 (0.4)	0	0	10 (3.5)	1 (0.4)	0	0
Alanine aminotransferase increased	8 (2.8)	6 (2.1)	8 (2.8)	3 (1.0)	9 (3.2)	7 (2.5)	8 (2.8)	3 (1.0)
Decreased appetite	9 (3.2)	1 (0.4)	2 (0.7)	0	9 (3.2)	1 (0.4)	2 (0.7)	0
Blood creatinine increased	7 (2.5)	4 (1.4)	0	0	8 (2.8)	4 (1.4)	0	0
Hypokalaemia	8 (2.8)	6 (2.1)	0	0	8 (2.8)	6 (2.1)	0	0
Acute kidney injury	6 (2.1)	2 (0.7)	1 (0.3)	1 (0.3)	6 (2.1)	2 (0.7)	1 (0.3)	1 (0.3)
Aspartate aminotransferase increased	5 (1.8)	3 (1.1)	6 (2.1)	2 (0.7)	6 (2.1)	4 (1.4)	6 (2.1)	2 (0.7)
Hyponatraemia	6 (2.1)	6 (2.1)	1 (0.3)	1 (0.3)	6 (2.1)	6 (2.1)	1 (0.3)	1 (0.3)
Dysgeusia	5 (1.8)	0	2 (0.7)	0	5 (1.8)	0	2 (0.7)	0
Weight decreased	5 (1.8)	2 (0.7)	1 (0.3)	0	5 (1.8)	2 (0.7)	1 (0.3)	0
Abdominal pain	4 (1.4)	1 (0.4)	0	0	4 (1.4)	1 (0.4)	0	0
Amylase increased	4 (1.4)	3 (1.1)	6 (2.1)	4 (1.4)	4 (1.4)	3 (1.1)	6 (2.1)	4 (1.4)
Anaemia	3 (1.1)	2 (0.7)	0	0	4 (1.4)	2 (0.7)	0	0
Headache	4 (1.4)	1 (0.4)	0	0	4 (1.4)	1 (0.4)	0	0
Neutropenia	4 (1.4)	4 (1.4)	2 (0.7)	2 (0.7)	4 (1.4)	4 (1.4)	2 (0.7)	2 (0.7)
Osteonecrosis of jaw	2 (0.7)	0	0	0	4 (1.4)	1 (0.4)	1 (0.3)	1 (0.3)
Dehydration	3 (1.1)	1 (0.4)	0	0	3 (1.1)	1 (0.4)	0	0
Erythema	3 (1.1)	1 (0.4)	0	0	3 (1.1)	1 (0.4)	0	0
Gamma-glutamyltransferase increased	3 (1.1)	3 (1.1)	3 (1.0)	3 (1.0)	3 (1.1)	3 (1.1)	3 (1.0)	3 (1.0)
Hypersensitivity	2 (0.7)	0	0	0	3 (1.1)	0	0	0
Pneumonia	2 (0.7)	1 (0.4)	3 (1.0)	3 (1.0)	3 (1.1)	1 (0.4)	4 (1.4)	3 (1.0)
Rash macular	3 (1.1)	2 (0.7)	0	0	3 (1.1)	2 (0.7)	0	0
Urinary tract infection	3 (1.1)	1 (0.4)	0	0	3 (1.1)	1 (0.4)	0	0
Dyspepsia	3 (1.1)	0	0	0	2 (0.7)	0	0	0
Dyspnoea	1 (0.4)	0	3 (1.0)	2 (0.7)	1 (0.4)	0	3 (1.0)	2 (0.7)
Hyperkalaemia	0	0	3 (1.0)	3 (1.0)	0	0	3 (1.0)	3 (1.0)
Rash generalized	4 (1.4)	1 (0.4)	0	0	0	0	0	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 21.1 (safety update 1) and version 22.1 (safety update 2); CTCAE version 4.03.
Source: SCS Appendix 3-Table 14.3.1-1.10su, [SCS Appendix 5-Table 14.3.1-1.10]

2.6.1. Discussion on clinical safety

The clinical safety data submitted in support of this marketing authorisation application consisted of the whole set of patients included in Study C2301 (SOLAR-1), pooling both PIK3CA-mutant and non-mutant cohorts, and data from the dose-finding studies X2101 and X1101.

As of the 12 June 2018 data cut-off, the median duration of exposure for the study treatment was 8.2 months in the alpelisib arm and 5.6 months in the placebo arm. However, median exposure for alpelisib only was 5.5 months. The median relative dose intensities of alpelisib and placebo were 83.4% and 100%, respectively. During the procedure, updated safety data with a longer follow-up were provided (DCO 20 Oct 2018; 30 Sep 2019). As of the 30 September 2019 data cut off, approximately, 28% of patients were exposed to alpelisib for at least 12 months and around 13% of patients for at least 24 months. Overall, the safety profile of alpelisib plus fulvestrant at the DCO 30 Sep 2019 remained consistent with the previous safety update (DCO 20 Oct 2018) and with the original submission (DCO 12 Jun 2018).

In spite of the lack of shared toxicities between PIK3 inhibitors and fulvestrant, dose interruptions more than doubled in the experimental arm and dose reductions were multiplied by a factor 8.

In marked contrast with less-specific PIK3 inhibitors, there were no reports of hepatic and neuropsychiatric safety issues which suggest that the higher selectivity of alpelisib may be successful. However, this may change with updated safety data with relevant exposure. The applicant will provide further long-term safety data with the final CSR of SOLAR-1 study (see Annex II condition).

The combination of alpelisib plus fulvestrant was more toxic than fulvestrant monotherapy. Treatment-related grade 3 and 4 AEs were six times as frequent (66.9% vs. 11.8%), and SAEs doubled (36.6% vs. 18.8%), requiring significantly more treatment discontinuations (26.1% vs. 5.6%) and dose modifications (79.2% vs. 23%) (DCO 30 Sep 2019).

AEs of any grade reported in over 20% of cases with alpelisib plus fulvestrant therapy in Study C2301 (DCO30 Sep 2019) were, in order of the difference magnitude between arms (alpelisib vs. placebo): weight decreased (27.8% vs. 2.4%), hyperglycaemia (64.8% vs. 9.4%), rash (36.3% vs. 7%), stomatitis (25% vs. 7%), diarrhoea (59.5% vs. 16.4%), decreased appetite (35.9% vs. 10.5%), vomiting (28.5% vs. 10.1%), nausea (46.8% vs. 22.6%), asthenia (22.2% vs. 13.6%), and fatigue (25% vs. 17.8%). Most serious issues were diarrhoea, rash and hyperglycaemia, all of them reaching grade 3 in a significant fraction of patients and being responsible for the vast majority of treatment delays and dose modifications. The grade 4 AE registered in more patients was hyperglycaemia, with eleven cases in the alpelisib arm (11 [3.9%] alpelisib vs. 1 [0.3%] placebo) (DCO 30 Sep 2019).

The safety profile of fulvestrant monotherapy is well known and data from the pivotal trial is consistent with this knowledge.

Adverse events of special interest included gastrointestinal (GI) toxicity, hyperglycaemia, rash, hypersensitivity, pancreatitis, pneumonitis, severe cutaneous reactions and osteonecrosis of the jaw (ONJ).

Osteonecrosis of jaw (ONJ) was reported in a high number of patients in the alpelisib arm compared to the placebo arm (16 [5.6%] vs 5 [1.7%]). All these events, except one in the placebo group, occurred in patients who had received concomitant therapy with bisphosphonate or denosumab (prior or after initiation of study drug) (130 [45.8%] in the alpelisib arm and 136 [47.4%] in the placebo arm). While the contribution of alpelisib to the development of ONJ is not completely clear, an increased risk of development of ONJ cannot be excluded in patients receiving alpelisib and bisphosphonates. ONJ is included as a common adverse drug

reaction in section 4.8 of the SmPC and as an important identified risk in the RMP. The risk of ONJ falls under the primary objective of safety in the European study CBYL719A0IC02 included as a category 3 study in the RMP. Furthermore, a warning has been included in section 4.4 of the SmPC to inform that caution should be exercised when Piqray and bisphosphonates or denosumab are used either simultaneously or sequentially. Piqray treatment should not be initiated in patients with ongoing osteonecrosis of the jaw from previous or concurrent treatment with bisphosphonates/denosumab. Patients should be advised to promptly report any new or worsening oral symptoms (such as dental mobility, pain or swelling, non-healing of mouth sores, or discharge) during treatment with Piqray. In patients who develop osteonecrosis of the jaw, standard medical management should be initiated (see SmPC section 4.4).

Rash and GI toxicities were not dissimilar to what is commonly experienced with several anti-cancer targeted agents. Although both were more common in the alpelisib arm (six-fold and two-fold, respectively), most cases were grade 1 or 2 and rarely the cause for discontinuation. Nevertheless, cases of severe cutaneous reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme (EM), were reported in patients treated with alpelisib in clinical studies. In study C2301, SJS and EM were reported in 1 (0.4%) and 3 (1.1%) patients, respectively. Moreover, drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post-marketing setting (see SmPC sections 4.2 and 4.8). Severe cutaneous reactions are included as an important identified risk in the risk management plan (RMP). Section 4.8 of the SmPC has also been updated to reflect that serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested by symptoms including, but not limited to, dyspnoea, flushing, rash, fever or tachycardia, were reported in patients treated with alpelisib in clinical studies (see SmPC section 4.8).

Patients should be advised of the signs and symptoms of severe cutaneous reactions (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of severe cutaneous reactions are present, alpelisib should be interrupted until the aetiology of the reaction has been determined. Appropriate treatment should be promptly initiated (see SmPC section 4.4). A consultation with a dermatologist is recommended. If a severe cutaneous reaction is confirmed, Piqray should be permanently discontinued. Piqray should not be re-introduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, Piqray may require treatment interruption, dose reduction or treatment discontinuation as described in Table 3 of the SmPC (see SmPC sections 4.2 and 4.4).

Furthermore, alpelisib treatment should not be initiated in patients with a history of severe cutaneous reactions (see SmPC section 4.4).

Hypersensitivity to the active substance or to any of the excipients is also a contraindication (see SmPC section 4.3).

With regards to the event of rash, among patients who received prophylactic anti rash treatment including antihistamines, rash was reported less frequently than in the overall population. Accordingly, oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with Piqray. Additionally, antihistamines are recommended to manage symptoms of rash. Furthermore, topical corticosteroid treatment should be initiated at the first signs of rash and oral corticosteroids should be considered for moderate to severe rashes. Based on the severity of rash, Piqray may also require dose interruption, reduction or discontinuation as described in Table 3 of the SmPC (see SmPC sections 4.2 and 4.8).

Two patients suffered from diarrhoea and associated dehydration, which may have contributed to the development of acute kidney injury. In both cases, the treatment was temporarily interrupted, and the events resolved, but this was a potentially fatal situation. GI toxicity was observed to a similar extent in the supportive phase 1 study. This type and severity of GI toxicity is considered to have adverse clinical impact on the patient's well-being and require adequate monitoring. Based on the severity of the diarrhoea, Piqray may require dose interruption, reduction or discontinuation as described in the SmPC (see SmPC sections 4.2 and 4.4). Patients should be advised to start antidiarrhoeal treatment, increase oral fluids and notify their physician if diarrhoea occurs while taking Piqray.

Hyperglycaemia is the main safety issue to be considered. Severe hyperglycemia, including ketoacidosis, has been reported in patients treated with Piqray. In the SOLAR-1 study, FPG and HbA1c security thresholds were not only built into the inclusion criteria but modified twice on the safe side in subsequent protocol amendments (amendment 1 and 2).

There was no separate study for type 2 diabetic patients, a clear group of interest given the high incidence and severity of hyperglycaemic events in the alpelisib plus fulvestrant arm. As patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II were excluded in Study C2301, it is reflected in the SmPC under section 4.4 that the safety of alpelisib in these patients has not been established. Patients with a medical history of Type 2 diabetes were included. The SmPC reflects that patients with a history of diabetes mellitus may require intensified diabetic treatment and should be closely monitored.

It appeared early in many cases and occurred in nearly 65% of the patients, reaching grade 3 or 4 in half of them despite specific treatment instituted in 52.8% of the affected patients plus dose interruptions and modifications in around 50% of the subjects. SAEs were observed in 30 patients (10.6%). The most frequent medication used was metformin (87.1%) and various types of insulin (31.9%). An oral treatment such as metformin is often more feasible than injections with insulin; however, metformin is associated with increased risk or worsening of diarrhoea, which is particularly harmful for patients on alpelisib due to the already high risk of diarrhoea. There were no deaths attributable to hyperglycaemia, complications such as ketoacidosis were exceptional but permanent discontinuation of treatment related to hyperglycaemia happened in 19 patients (6.7%), being the leading cause for treatment discontinuation.

The alpelisib-induced hyperglycaemia was reversible upon discontinuation of alpelisib treatment. In the setting of a clinical trial, this event may be manageable; however, in the clinical setting, hyperglycaemia and related events may be fatal if not timely diagnosed and treated. Baseline diabetic and pre diabetic status, baseline BMI ≥30 and baseline age ≥75 years have been found to be risk factors for hyperglycaemia and high-grade hyperglycaemia in patients treated with alpelisib. These risk factors were present in 74.7% of patients with any grade of hyperglycaemia and in 86.2% of patients with grade 3 or 4 hyperglycaemia. These numbers have been reflected in the SmPC under the headline hyperglycaemia in section 4.2, as they are very informative for both the treating physician and the patient. Furthermore, additional precautionary measures, monitoring, and handling of the risk of hyperglycaemia have been included in the product information (see sections 4.2 and 4.4). Dose interruption, reduction or discontinuation based on the severity of the hyperglycaemia are described in Table 2 of the SmPC.

As hyperglycaemia may occur with a rapid onset after starting treatment, it is recommended to self-monitor frequently in the first 4 weeks and especially within the first 2 weeks of treatment, as clinically indicated. A specific schedule for fasting glucose monitoring is recommended in Table 6 of the SmPC. All patients should be instructed on lifestyle changes that may reduce hyperglycaemia (e.g. dietary restrictions).

Patients should also be advised of the signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss).

In addition to routine risk minimisation measures, a prescribers' guide providing further guidance for the prevention and management of hyperglycaemia will be distributed to further minimise this risk (see RMP).

Additional pharmacovigilance activities are included in the RMP to further characterise the risk of hyperglycaemia. Study CBYL719C2402 is a retrospective cohort study in the US to evaluate the risk of hyperglycaemia in patients with advanced breast cancer treated with Piqray (alpelisib) in the real-world setting (Category 3 study in RMP). Next to this US based study on hyperglycaemia, study BYL719A0IC02 will be conducted in the EU to investigate general safety and risk of hyperglycaemia of alpelisib. This is an open-label, multicentre, Phase IIIb study to evaluate the safety and tolerability of alpelisib in combination with fulvestrant for the treatment of men and post-menopausal women with hormone receptor-positive (HR+), HER2-negative advanced breast cancer with a PIK3CA mutation, after disease progression following an endocrine-based regimen (Category 3 study in RMP).

Pancreatitis, hypersensitivity and anaphylactic reactions were subjected to increased supervision, but no worrying issues were observed. These risks have been reflected in the SmPC.

Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, have also been reported in alpelisib treated patients in clinical studies. Patients should be advised to report promptly any new or worsening respiratory symptoms. In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, alpelisib treatment should be interrupted immediately and the patient should be evaluated for pneumonitis. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, cough, dyspnoea, or interstitial infiltrates on radiological examination and in whom infectious, neoplastic and other causes have been excluded by means of appropriate investigations. Alpelisib should be permanently discontinued in all patients with confirmed pneumonitis (see SmPC section 4.4).

Deaths and SAEs were investigated in a pooled set combining data from studies C2301, X2101 and X1101. A review of the deaths did not identify any worrisome pattern. Most deaths were due to disease progression. Out of the pooled safety analysis of 725 patients, there was only a doubtful case of alpelisib-related death, an event of thrombotic microangiopathy reported in one patient in study C2301. The investigator considered this event may be related to study treatment, however since other contributing factors were present a clear relationship with alpelisib+fulvestrant treatment cannot be established.

Serious AEs were twice as frequent in the alpelisib plus fulvestrant group relative to the placebo plus fulvestrant group in Study C2301. But, except for hyperglycemia (9.9%), the incidence of specific individual SAEs was under 3% for both groups and under 1.5% when only grade 3/4 SAEs were considered.

Clinical chemistry abnormalities were mostly low-grade and/or evenly distributed in both arms, except for higher incidence of grade 3 hyperglycaemia in the alpelisib arm. Other laboratory abnormalities that occurred more frequently in the alpelisib plus fulvestrant group (≥10% difference) were increases in creatinine (66.9% vs 24.7%), increases in lipase (41.9% vs 25.4%) and decreases in potassium (13.7% vs 2.8%). Those abnormalities were mostly grade 1 or 2 and not related to SAEs, need for specific treatments, dose interruptions or dose modifications.

More patients in the alpelisib arm developed low haemoglobin (+12.4%), low platelets (+7.8%), and increased APTT (+5.4%). The haematological toxicity is related to the alpelisib treatment but is within an acceptable level.

Patients discontinued study treatment in a very high number of cases in the alpelisib arm (25.4% vs. 4.5%), most frequently due to hyperglycaemia (6.3%), rash (3.2%), diarrhea (2.8%), and fatigue (2.1%). It is noted that only half of the AEs leading to discontinuation were of high grade, leading to an assumption that maybe in these cases, it was the sum of several AEs and/or the required treatment for an AE (e.g. anti-diabetic medicine), that led to the discontinuation. In addition, most events were solved/reversible by discontinuation of alpelisib.

As only adults were included in the clinical studies, there are no safety data in children aged 0-18 years old.

Piqray is indicated in men and postmenopausal women and is not to be used in women who are, or may be, pregnant or breast feeding (see SmPC sections 4.1 and 4.6). Females of reproductive potential should be advised that animal studies and the mechanism of action have shown that alpelisib can be harmful to the developing foetus. Embryo-foetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity (see SmPC sections 4.6 and 5.3). In case females of reproductive potential take Piqray, they should use effective contraception (e.g. double barrier method) when taking Piqray and for at least 1 week after stopping treatment with Piqray.

Male patients with sexual partners who are pregnant, possibly pregnant or who could become pregnant should use condoms during sexual intercourse while taking Piqray and for at least 1 week after stopping treatment with Piqray.

There are no data from the use of alpelisib in pregnant women. Studies in animals have shown reproductive toxicity (see SmPC section 5.3). Therefore, alpelisib is not recommended during pregnancy and in women of childbearing potential not using contraception. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Piqray.

It is not known if alpelisib is excreted in human or animal milk. Because of the potential for serious adverse reactions in the breast-fed infant, it is recommended that women should not breast-feed during treatment and for at least 1 week after the last dose of Piqray (see SmPC section 4.6).

The adverse reactions associated with overdose have been consistent with the safety profile of Piqray and included hyperglycaemia, nausea, asthenia and rash. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary. There is no known antidote for Piqray (see SmPC section 4.9).

As fatigue or blurred vision during treatment have been reported with Piqray, this could affect the ability to drive or use machines (see section 4.8).

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC. Furthermore, adequate recommendations have been included in the SmPC with regards to the management of severe or intolerable adverse drug reactions (ADRs) which may require temporary dose interruption, reduction, and/or discontinuation. If dose reduction is required, the dose reduction guidelines for ADRs are listed in Table 1 of the SmPC. A maximum of 2 dose reductions are recommended, after which the patient should be permanently discontinued from treatment with Piqray. Dose reduction should be based on the worst preceding toxicity. As discussed further above additional tables (Tables 2-5) summarise the recommendations for dose interruption, reduction or discontinuation of Piqray in the management of specific ADRs. The clinical judgement of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with Piqray.

2.6.2. Conclusions on the clinical safety

The combination of alpelisib and fulvestrant is significantly more toxic than endocrine treatment but presumably less than chemotherapy, which is the treatment most study patients would probably have received if not included in the trial. In general terms, toxicity may be manageable, provided careful attention is paid to hyperglycaemia-related issues and GI toxicity such as diarrhoea, both in the selection of patients and during treatment.

2.7. Risk Management Plan

Safety concerns

Table 83: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hyperglycaemia Pneumonitis Severe cutaneous reactions Osteonecrosis of the jaw
Important potential risks	None
Missing information	Safety with long-term use

Pharmacovigilance plan

Table 84: Ongoing and planned additional pharmacovigilance activities

Study	**Summary of objectives**	**Safety concerns addressed**	**Milestones**
Study CBYL719C2402 A retrospective cohort study to evaluate the risk of hyperglycaemia in patients with advanced breast cancer treated with Piqray (alpelisib) in the real world setting. Category 3	The **primary objective** is to estimate the incidence of hyperglycemia (any severity, and severe hyperglycemia) in a cohort of men and postmenopausal women with HR-positive HER2-negative advanced breast cancer treated with alpelisib in combination with fulvestrant, following treatment with an endocrine-based regimen. The **secondary objectives** are, • To characterize time to hyperglycemia (any severity, and severe hyperglycemia) since alpelisib initiation among patients who developed such events. • To evaluate the impact of known risk factors of hyperglycemia in the real world setting.	Hyperglycaemia	Final report submission: 31-May-2023
BYL719A0IC02	**Primary objective:**	Hyperglycaemia	Final report submission:

Study	Summary of objectives	Safety concerns addressed	Milestones

An open-label, multicenter, Phase IIIb study to evaluate the safety and tolerability of alpelisib in combination with fulvestrant for the treatment of men and post-menopausal women with hormone receptor-positive (HR+), HER2-negative advanced breast cancer with a PIK3CA mutation, after disease progression following an endocrine based regimen.
 	
Category 3
	To evaluate the safety and tolerability of alpelisib plus fulvestrant.
	Secondary objective:
	• To assess the overall response rate (ORR) in patients with measurable disease
	• To assess alpelisib dose changes due to adverse events
	• To assess clinical benefit rate (CBR)
	• To assess duration of response (DOR) in patients with confirmed complete response (CR) or partial response (PR)
	• To assess risk factors for hyperglycemia
	• To assess the time to tumor progression (TTP) as per RECIST 1.1
	• To assess the treatment discontinuation rate
	• To evaluate change in global health status/QOL and pain (only in selected countries)
	• To evaluate effectiveness of additional risk minimization measures for hyperglycaemia by
	  • Analyzing all hyperglycaemia AESI events (serious and non-serious)
	  • Assessing HCP awareness of the content of educational material via HCP questionnaire
		Osteonecrosis of the jaw	31-Mar-2024

Risk minimisation measures

Table 85: Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hyperglycaemia	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2, 3, 4 Additional risk minimization measures: Prescriber's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study CBYL719C2402 Study BYL719A0IC02
Pneumonitis	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 PL Sections 2, 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	None Additional pharmacovigilance activities: None
Severe cutaneous reactions	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 PL Sections 2, 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Osteonecrosis of the jaw	Routine risk minimization measures: SmPC Sections 4.4, 4.8 PL Sections 2, 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up checklist Additional pharmacovigilance activities: Study BYL719A0IC02
Safety with long-term use	Currently available data are limited and do not support the need for risk minimization.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. 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 24 May 2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of alpelisib 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 alpelisib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication was for the treatment of postmenopausal women, and men with HR-positive, HER2-negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine-based regimen.

The aim of therapy in this setting is to reduce symptoms and prolong life while preserving quality of life.

3.1.2. Available therapies and unmet medical need

Endocrine therapy is the treatment of choice for patients with HR-positive advanced breast cancer (ABC). Endocrine therapies include selective ER modulators (tamoxifen), selective nonsteroidal aromatase inhibitors (letrozole and anastrozole), steroidal AIs (exemestane), and ER antagonists (fulvestrant). It may be given in first, second, or later lines of therapy for advanced breast cancer (NCCN 2018, ESMO Guideline). Progressive disease ultimately develops in all patients, either due to primary resistance or relapse/progression following an initial response.

De novo or acquired endocrine resistance remains an unsolved clinical issue. Once ABC progresses to hormonal 1st line there are basically three options to choose from: 1) switch to another not previously used endocrine-based treatment, 2) proceed to chemotherapy or 3) turn to one of the novel targeted therapy-based combinations.

Two targeted strategies are now commercially available in the EU for the treatment of women with locally advanced or metastatic HR-positive HER2-negative BC after a previous endocrine treatment: cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib and abemaciclib), and inhibitors of the mechanistic target of rapamycin (mTOR) (everolimus). CDK 4/6 inhibitors are approved in combination with either an aromatase inhibitor or fulvestrant, while mTOR-inhibitor everolimus is only approved in combination with the aromatase inhibitor AI exemestane.

The targeted patient population has a rather good prognosis despite the palliative setting with no chance of curability, as the median OS is approximately 42 months (Gobbini EJC 2018). This means that some of these patients with advanced breast cancer, especially those with bone metastases only, may survive for more than 10 years. As this disease ultimately causes death within a limited number of years, there exist an unmet medical need for new treatment options, especially treatments that can prolong time on endocrine-based regimens. Nevertheless, it should be kept in mind that numerous treatment options already exist for this patient population.

3.1.3. Main clinical studies

The main evidence in support of this application is a randomized, double-blind, international, multicentre placebo-controlled phase III study (SOLAR-1) evaluating alpelisib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer who progressed on or after aromatase inhibitor treatment.

3.2. Favourable effects

In the pivotal study SOLAR-1, treatment with alpelisib in combination with fulvestrant prolonged PFS (as assessed by the investigator) in patients with PIK3CA mutant advanced breast cancer (n=341), with hazard ratio (HR) 0.65 (95% CI: 0.50, 0.85; p-value: 0.00065). The median PFS was 11.0 months (95% CI: 7.49, 14.52) in the alpelisib plus fulvestrant arm versus 5.7 months (95% CI: 3.65, 7.36) in the placebo plus fulvestrant arm, with a difference in median of 5.3 months between arms.

These results were supported by a blinded independent central review (BIRC), performed on a randomly selected subset of 50% of randomised patients with a HR of 0.48 (95% CI: 0.32, 0.71) and a median PFS of 11.1 months (95% CI: 7.33, 16.76) in the alpelisib versus 3.7 months (95% CI: 2.07, 5.55) in the placebo arm.

OS data are immature with 27% events (23.7% events in the experimental arm and 30.2% events in the control arm). However, no detrimental effect is observed based on the available data.

ORR in the subset of patients with measurable disease at baseline (n=262) was 35.7% (95% CI: 27.4, 44.7) and 16.2% (95% CI: 10.4, 23.5), in the experimental and control arm, respectively.

3.3. Uncertainties and limitations about favourable effects

OS data are immature. In order to further investigate the efficacy alpelisib in combination with fulvestrant in the target population, the MAH will submit the final study report of the phase III randomized placebo controlled study SOLAR-1 including interim and final analyses of overall survival by 31 August 2022 (PAES).

Patients included in the study SOLAR-1 should have radiological or objective evidence of recurrence or progression during or after AI therapy. It is noted that patients included in the pivotal trial for alpelisib were generally endocrine-resistant (87% are considered resistant to prior endocrine therapy). Almost no patients previously exposed to fulvestrant were included in the phase III trial. However, in the supportive study X2101, a few patients with measurable disease at baseline and previously treated with fulvestrant obtained a partial response from the alpelisib-based treatment, which could support the idea that the previous exposure to fulvestrant would not impair the antitumor activity of the combination of alpelisib-fulvestrant. Likewise, from a mechanistically perspective, there would not be any reason of such a possibility. Nevertheless, no firm conclusion can be drawn due to the limited number of patients with prior fulvestrant use. This has been reflected in the SmPC (see SmPC section 4.4 and 5.1).

Furthermore, in the SOLAR-1 study the total number of patients pre-treated with a CDK4/6 inhibitor was predefined to be limited to 30% of the overall study population based on the concern at the time of the initial protocol, mid-2015, that prior treatment with a CDK4/6 inhibitor may impact the outcome of subsequent treatment with PI3K inhibitors compared to CDK4/6 inhibitor naive subjects. In total, only 20 patients with prior CDK 4/6 inhibitors treatment were included in the SOLAR-1 study (9 patients in the alpelisib arm and 11 patients in the control arm) hampering any conclusion on the efficacy of alpelisib in combination with fulvestrant in this subgroup. Further data were provided from cohort A of the BYLieve study which included 121 subjects previously exposed to CDK4/6 inhibitors. In this cohort, in patients with measurable disease, the ORR was 21%and the DOR was 6.6 months (95%CI: 4.3; NE), whereas in the PIK3CA mutant cohort within the SOLAR-1 study in patients with measurable disease, the ORR in the treatment arm with the combination of alpelisib plus fulvestrant regardless of the prior treatment (n=169) was 35.7%(95%CI: 27.4, 44.7) and the DOR 12.6 months (95%CI: 8.5; 18.5). Due to the design of the study BYLieve it is not possible to isolate the contribution of fulvestrant, so efficacy in this sub-population is not considered established.

Overall, there is insufficient evidence to conclude on the efficacy of alpelisib in combination with fulvestrant in patients previously treated with CDK4/6 inhibitors. For that reason, it is recommended to restrict the indication restricted to patients previously treated with endocrine therapy as monotherapy.

3.4. Unfavourable effects

Overall, the most commonly reported AEs in patients treated with alpelisib plus fulvestrant were plasma glucose increased (79.2%), creatinine increased (67.6%), diarrhoea (59.5%), gamma glutamyltransferase increased (53.2%), rash (51.8%), lymphocyte count decreased (55.3%), nausea (46.8%), alanine aminotransferase increased (44.0%), anaemia (44.0%), fatigue (43.3%), lipase increased (42.6%), decreased appetite (35.9%), stomatitis (30.3%), vomiting (28.5%), weight decreased (27.8%), hypocalcaemia (27.8%), plasma glucose decreased (26.8%), activated partial thromboplastin time (aPTT) prolonged (22.2%) and alopecia (20.4%).

Grade 3-4 AEs were reported by 77.5% of patients in the alpelisib plus fulvestrant arm compared to 36.6% of patients in the placebo plus fulvestrant arm. Hyperglycaemia (37% vs. 1%) and diarrhoea (7% vs. 0.7%) were the most frequent Grade 3-4 AEs in the alpelisib group.

SAEs were reported by 36.6% of patients treated with alpelisib plus fulvestrant and 18.8% of those that received placebo plus fulvestrant. In the alpelisib arm most of the SAEs were considered treatment-related (22.5% vs. 1.7%, experimental and control arm, respectively).

With regard to deaths, 78 (27.5%) patients in the experimental arm and 91 (31.7%) patients in the control arm died (cut-off date 12 Jun 2018). The majority of deaths were due to disease progression in both treatment arms (74 and 79, respectively). Of the remaining deaths, 4 (1.41%) in the alpelisib arm and 12 (4.18%) in the placebo arm were due to other cause. Of these 4 deaths in the alpelisib arm, 2 occurred post treatment (thrombotic microangiopathy, which was suspected to be related to study treatment, and sepsis) and the other 2 deaths occurred while on-treatment (cardio-respiratory arrest and second primary malignancy). In a safety update (cut-off date 20 Oct 2018), the total number of deaths increased to 96 (33.8%) in the alpelisib plus fulvestrant group, and 101 (35.2%) in the placebo plus fulvestrant group. Of the 18 additional post-treatment deaths in the alpelisib plus fulvestrant group, 16 deaths were due to breast cancer / disease progression. The two remaining additional post-treatment deaths were due to septic shock and unknown cause. Both deaths occurred more than a year after the last dose of study drug. In a second safety update (cut-off date 30 Sep 2019), the total number of deaths was 128 (45.1%) in the alpelisib plus fulvestrant group, and 142 (49.5%) in the placebo plus fulvestrant group. Most of these deaths were due to the study indication (119 (41.9%) in the alpelisib plus fulvestrant group, and 128 (44.6%) in the placebo plus fulvestrant group).

Discontinuations due to AEs were required in 26.1% of patients treated with alpelisib plus fulvestrant compared with 5.6% of patients that received placebo plus fulvestrant. In the alpelisib arm, hyperglycaemia (6.3%), rash (3.2%), diarrhoea (2.8%) and fatigue (2.1%) were the main AEs that led to treatment discontinuation. Additionally, 79.2% and 23% of patients in the alpelisib and placebo group, respectively, required dose reductions or dose interruptions.

Overall, the main AEs for alpelisib considered of special interest were hyperglycaemia, rash and severe cutaneous reactions, gastrointestinal toxicity, hypersensitivity and anaphylactic reactions, pancreatitis and pneumonitis. In the alpelisib arm, 66.9% of patients had a hyperglycaemia AESI, which were grade 3 for 33.8% and grade 4 for 4.6% of the patients. SAEs were observed in 30 patients (10.6%). Hyperglycaemia required medication or therapy for 58.1% and lead to permanent discontinuation in 6.3%.

It is noted that less than half of the patients (41.2%) could avoid anti-diabetic treatment in case of hyperglycaemia. The alpelisib-induced hyperglycaemia was reversible upon discontinuation of alpelisib treatment.

Skin-related events were observed in 72.9% of patients in all grades and events of grade 3/4 in 22.2% of the patients treated with alpelisib. Cases of SJS and EM were reported in 1 (0.4%) and 3 (1.1%) of patients treated with alpelisib, respectively.

3.5. Uncertainties and limitations about unfavourable effects

Tolerability of alpelisib treatment in combination with fulvestrant appears to be low based on the high rate of discontinuations (a quarter of the patients discontinued study drug in the study SOLAR-1), which might be higher in the clinical setting.

Safety with long-term use is limited and has been included as missing information in the RMP. Long-term safety assessment will be provided with the final CSR of study C2301.

Additionally, there was no separate study for type 2 diabetic patients, a clear group of interest given the high incidence and severity of hyperglycaemic events in the alpelisib plus fulvestrant arm. Moreover, patients with type 1 diabetes or those with uncontrolled type 2 diabetes were not included in the clinical trial. This information has been reflected in the SmPC, section 5.1.

3.6. Effects Table

Table 86: Effects Table for alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative, advanced breast cancer with PIK3CA mutation – Study SOLAR-1 (data cut-off: 12 Jun 2018)

Effect	Short Description	Unit	Alpelisib + fulvestrant	Placebo + fulvestrant	Uncertainties/ Strength of evidence	References
Favourable Effects[a]						
PFS	Progression free survival (investigator)	Median, months (95% CI)	11.0 (7.4, 14.5)	5.7 (3.7, 7.4)	HR 0.65 (95% CI: 0.50, 0.85); one-sided p=0.00065.	Clinical efficacy section, SOLAR-1 study report
OS	Overall survival	Median, months (95% CI)	40.6 (32.2, NE)	31.2 (26.8, NE)	HR 0.77 (95% CI: 0.56, 1.06); one-sided p=0.06 Second interim analysis. The pre-specified stopping boundary was p≤0.00121	
ORR	Overall response rate (investigator)	Proportion (%)	26.6	12.8	ORR in patients with measurable disease at baseline was 35.7% and 16.2%, treatment and control arm, respectively	
Unfavourable Effects[b]						

Effect	Short Description	Unit	Alpelisib + fulvestrant	Placebo + fulvestrant	Uncertainties/ Strength of evidence	References
Grade 3-4	Incidence of adverse events of grade 3 or 4	Proportion (%)	77.5	36.6		Clinical safety section, SOLAR-1 study report
SAEs	Incidence of serious adverse events	Proportion (%)	36.6	18.8		
Discontinuations	Incidence of discontinuations due to adverse events	Proportion (%)	26.1	5.6		
Hyperglycaemia	Common adverse event	Proportion (%)	64.8	9.4		
Diarrhoea	Common adverse event	Proportion (%)	59.5	16.4		
Nausea	Common adverse event	Proportion (%)	46.8	22.6		
Decreased appetite	Common adverse event	Proportion (%)	35.9	10.5		
Rash	Common adverse event	Proportion (%)	36.3	7.0		
Osteonecrosis of jaw	Adverse event of special interest	Proportion (%)	5.6	1.7		
Pneumonitis	Adverse event of special interest	Proportion (%)	1.8	0.3		
Severe cutaneous reactions	Adverse events of special interest	Proportion (%)	1.4	0		

Abbreviations: HR (hazard ratio), HER2 (epidermal growth factor receptor 2), NE (not estimable)
Notes: [a] Efficacy data were estimated in the Full Analysis Set, PIK3CA mutant cohort (n=341). [b] Safety data are based on the 571 patients treated in study SOLAR-1 (Data cut-off: 30 Sep 2019)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Alpelisib in combination with fulvestrant has demonstrated a clinically relevant delay in progression free survival in the PIK3CA mutant cohort in comparison to fulvestrant alone. This was supported by several sensitivity analyses as well as by the higher antitumor activity shown in the combination arm versus the monotherapy group.

Considering the limited number of patients with prior treatment based on CDK4/6 inhibitors included in the pivotal study, this does not provide direct evidence for clinical benefit in such patients. The extrapolation of efficacy is questionable based on the outcomes of the single arm study BYLieve, in patients with prior CDK4/6 experience. The objective response rate and duration of response observed in this study, cannot be readily translated into clinical benefit, and would not have supported such an inference on their own; contrariwise, they are indicative that the efficacy of fulvestrant and alpelisib may be considerably reduced in the post

CDK4/6 setting, and it is not clear that the B/R would be positive. Therefore, available data do not support an indication covering patients with PIK3CA mutation previously treated with CDK 4/6 inhibitors.

From a safety point of view, tolerability of alpelisib plus fulvestrant seems to be low, according to the high rate of discontinuations, mainly due to hyperglycaemia. Hyperglycaemia, GI toxicity and skin-related events are adverse events of special interest related to alpelisib. Overall, the combination of alpelisib and fulvestrant is considered to be significantly more toxic than endocrine treatment but presumably less than chemotherapy which is the treatment most study patients would probably have received if not included in the trial.

In general terms, toxicity may be manageable, provided careful attention is paid to hyperglycaemia-related issues and GI toxicity such as diarrhoea, both in the selection of patients and during treatment.

3.7.2. Balance of benefits and risks

Alpelisib in combination with fulvestrant leads to a longer PFS in HR-positive, HER2-negative, locally advanced or metastatic breast cancer patients with a PIK3CA mutation in the ITT population. While this clinically meaningful benefit may be extrapolated to patients having progressed on any endocrine therapy given in monotherapy, based on limited data and mechanistic rationality, efficacy has not been established in the subpopulation of patients who previously have received CDK4/6 inhibitors in combination with endocrine therapy.

Overall, the favourable effects are considered to outweigh the risks associated with the treatment of alpelisib in combination with fulvestrant in patients previously treated with endocrine therapy in monotherapy.

3.7.3. Additional considerations on the benefit-risk balance

Considering the limited efficacy data available in patients pre-treated with CDK4/6 inhibitors as well as the outcome of the BYLieve study, a positive benefit-risk has not been established in this sub-population, which has thus been excluded from the recommended indication.

3.8. Conclusions

The overall B/R of Piqray in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, is positive.

Divergent position is appended to this report.

4. Recommendations

Outcome

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

Piqray is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine

therapy as monotherapy.

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.

Additional risk minimisation measures

Prior to launch of Piqray in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of severe hyperglycaemia, including ketoacidosis, and how to manage them.

The MAH shall ensure that in each Member State where Piqray is marketed, all healthcare professionals who are expected to prescribe Piqray have access to/are provided with the physician educational material.

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

Prior to initiating treatment

- Piqray is associated with an increased risk of hyperglycaemia.
- Patients at higher risk (diabetic, pre-diabetic, FPG >250 mg/dl, BMI ≥30, or age ≥75 years) need consultation with a healthcare professional experienced in the treatment of hyperglycaemia.
- The patient's current antidiabetic treatment might be affected by the treatment with alpelisib through interaction with oral antidiabetics metabolised by CYP2C9 and CYP2C8 (including, but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide).
- Test for FPG and HbA1c and optimise the patient's level of blood glucose before starting treatment with alpelisib.
- Counsel patients with regard to the risk of hyperglycaemia, need for lifestyle changes, signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss; difficulty breathing, headache, nausea, vomiting) and the importance of immediately contacting a healthcare professional if symptoms occur.

During treatment

- Follow the schedule for monitoring fasting glucose according to the Piqray label. Please note there are different schedules for patients with and without risk factors.
- In case of hyperglycaemia follow the hyperglycaemia-related dose modification and management table according to the Piqray label.
- When initiating antidiabetic treatment, consideration should be taken with regard to possible drug-drug interactions.

Obligation to conduct post-authorisation measures

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

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy and long-term safety of alpelisib in combination with fulvestrant in postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy, the MAH should submit the final study report of the phase III randomised placebo-controlled study CBYL719C2301 (SOLAR-1).	31 August 2022

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

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

New Active Substance Status

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

Appendix

1. Divergent positions to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 28 May 2020

DIVERGENT POSITION DATED 28 May 2020

Piqray EMEA/H/C/004804/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Piqray indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

The reason for divergent opinion was the following:

- The positive B/R of Piqray was established in the primary analysis population of the SOLAR-1 study, including patients previously treated with endocrine therapy. The number of patients included in the study that had received endocrine therapy in combination with a CDK4/6 inhibitor is small, and does not allow for an independent inference of efficacy in this subpopulation. However, there are no known mechanisms of resistance that would indicate that the efficacy demonstration for Piqray in the primary analysis would not be relevant to such patients.
- Furthermore, data from the single arm BYlieve study are available in the post CDK4/6 setting. Antitumoral activity in this study is not outstanding, and the BYlieve study could not independently have established the efficacy of Piqray. However, activity in terms of ORR appears similar to that seen for other drugs for which benefits on PFS and/or OS have been established in RCTs of the treatment of metastatic breast cancer.
- In conclusion, the indication of Piqray should not be limited to those patients that have not received a CDK4/6 inhibitor in combination with prior endocrine therapy.

CHMP Member expressing a divergent position:

Sol Ruiz

Maria Concepcion Prieto Yerro

Christophe Focke

Alexandre Moreau

Bruno Sepodes

Kristina Dunder

Johann Lodewijk Hillege

John Joseph Borg

Bjorg Bolstad (Norway)