EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2026
EMADOC-1700519818-3389467
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Piqray

International non-proprietary name: Alpelisib

Procedure No. EMA/VR/0000317159

Note

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

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BIRC	Blinded Independent Review Committee
BMI	Body mass index
BOR	Best overall response
BPI-SF	Brief Pain Inventory-Short Form
bpm	Beats per minute
CBR	Clinical benefit rate
CDK	Cyclin dependent kinase
CDx	Companion Diagnostics
CI	Confidence interval
CISH	Chromogenic in situ hybridization
COA	Clinical Outcome Assessments
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CRS	Case Retrieval Strategy
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor Deoxyribonucleic Acid
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDC	Electronic data capture
EDR	Early discordance rate
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End-of-treatment
EQ-5D-5L	EuroQoL 5-level instrument
ET	Endocrine therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
GGT	Gamma-glutamyl transferase
HER	Human epidermal growth factor receptor
HR	Hazard ratio
i.m.	Intramuscular
ICF	Informed consent form
IHC	Immunohistochemistry
IRT	Interactive Response Technology
ITT	Intent-to-treat
LDR	Late discordance rate
LVEF	Ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Magnetic Resonance Angiography
MRI	Magnetic resonance imaging
mTOR	Mammalian Target of Rapamycin
MUGA	Multigated acquisition
ORR	Overall response rate
OS	Overall survival
p.o.	orally
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival

PFS2	Progression on next line treatment or death from any cause
PgR	Progesterone receptor
PI3K	Phosphatidylinositol 3-kinase
PI3K	Phosphatidylinositol-3-Kinase
PIK3CA	Phosphoinositide-3-kinase catalytic subunit alpha
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of Life
QTLs	Quality tolerance limits
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
ESAE	Serious adverse event
SC	Steering Committee
SERD	Selective estrogen receptor degrader
SISH	Silver-enhanced in situ hybridization
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TTR	Time to response
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 05 December 2025 an application for a variation.

The following variation was requested:

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication for 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 an endocrine-based regimen; based on the primary analysis (DCO 15-Oct-2024) from the Phase III Study CBYL719C2303 (C2303, EPIK-B5). This is a Phase III, randomized, double-blind, placebo-controlled study of alpelisib (BYL719) in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor. As a consequence, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) 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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25/02/2021 (EMA/SA/0000050283). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Carolina Prieto Fernandez Co-Rapporteur: N/A

The PRAC Rapporteur was:

Timetable	Actual dates
Submission date	05 Dec 2025
Start of procedure:	24 Jan 2026
CHMP Rapporteur's preliminary assessment report circulated on:	20 Mar 2026
PRAC Rapporteur's assessment report circulated on:	24 Mar 2026
PRAC RMP advice and assessment overview adopted by PRAC	10 Apr 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 Apr 2026
MAH's responses submitted to the CHMP on:	21 May 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 Jun 2026
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	01 Jul 2026
CHMP opinion:	23 July 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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.

Epidemiology

Globally, breast cancer is the most common cancer type among women and the second most common cancer type overall. An estimated 2.3 million new breast cancer cases and 670 000 breast cancer-related deaths occurred worldwide in 2022. Most breast cancer cases and deaths occur in individuals aged 50 years and older, who account for 71% of new cases and 78% of deaths (Kim J et al, 2025).

In the EU, among females, breast cancer is the second more frequent cancer, with an age-standardised rate of 12.3/100.000 (around 10.4%) (Santucci et al, 2026).

In men, breast cancer is a rare condition constituting < 1% of all breast cancer diagnoses (Siegel et al, 2019).

Biologic features

Breast cancer can be categorized into different histopathologic subtypes based on the expression of the estrogen receptor (ER), the progesterone receptor (PR), and HER2 receptor overexpression. The predominant subset of breast cancer is HR-positive, HER2-negative that accounts for 65% to 75% of female breast cancer and 80% to 90% of male breast cancer (Tarantino P et al, 2020, Deniziaut G et al, 2022).

Approximately 40% of the tumors in patients with HR-positive, HER2-negative advanced breast cancer harbor a PIK3CA mutation (Fillbrunn M. et al[8], 2022).

Clinical presentation, diagnosis and stage/prognosis

Patients with HR-positive, HER2-negative advanced breast cancer with tumours harboring a PIK3CA mutation are associated with higher rates of chemotherapy resistance and. Studies indicate a short median PFS after CDK4/6 inhibitor-based therapy in these patients. Preclinical data suggest that the PI3K pathway mediates CDK4/6 inhibitor resistance, with acquired PIK3CA mutations possibly playing a role in this resistance. Patients with HR-positive, HER2-negative breast cancer whose tumor harbors a PIK3CA mutation and who progressed on endocrine-based regimens, including those with a CDK4/6 inhibitor, have a poor prognosis and limited treatment options (Fillbrunn M. et al, 2022, Yan M. et al, 2025).

Management

The ESMO guidelines recommend endocrine therapy in combination with a CDK4/6 inhibitor as the regimen of choice for the first line treatment of HR-positive, HER2-negative advanced breast cancer in patients without imminent organ failure. Chemotherapy is the preferred option in patients with imminent organ failure.

Alpelisib is recommended by ESMO in patients who relapse and whose tumours harbour a PIK3CA mutation, which in the EU is only approved for patients who received endocrine-therapy as monotherapy as first-line treatment. Similarly to the approach in the first-line, chemotherapy is the preferred option for patients who have imminent organ failure. The choice of chemotherapy or further endocrine-based therapy should be based on disease aggressiveness, extent and organ function and the associated toxicity profile.

Some new therapies specifically targeting PIK3CA have recently been approved in this setting: inavolisib (PIK3CA inhibitor authorised in July 2025) and capivasertib (AKT inhibitor authorised in June 2024). Inavolisib is authorised in combination with palbociclib and fulvestrant, for the treatment of adult patients with PIK3CA-mutated, oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment. Capivasertib is indicated in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen. Of these two new targeted therapies, only capivasertib is approved for use in a population similar to that for which alpelisib is authorised.

Although several treatment options exist for patients with HR-positive, HER2-negative, advanced breast cancer after disease progression on an endocrine-based regimen, this disease ultimately causes death within a limited number of years (Gennari et al., 2021). Thus, there exists an unmet medical need for new treatment options, particularly treatments that can prolong time on endocrine-

based regimens and treatments targeting tumours harbouring gene mutations associated to a poorer prognosis.

2.1.2. About the product

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.

Piqray is approved 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 new/extended claimed indication 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 an endocrine-based regimen*** *(see section 5.1* ***and for biomarker based patient-selection see section 4.2****)*".

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

The MAH received Scientific Advice on the development of alpelisib for the treatment of HR+, HER2- metastatic breast cancer from the CHMP on 25/02/2021 (EMA/SA/0000050283). The Scientific Advice pertained to the following clinical aspects:

Acceptability of Study C2303 and the proposed statistical analysis plan to support a regulatory filing, in particular with regards to statistical considerations for the endpoints and primary estimand.

2.1.4. General comments on compliance with GCP

The MAH has claimed that the development program has been conducted as per GCP.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

An updated Environmental Risk Assessment has been provided in which the environmental data submitted as part of the initial MAA has been used (EMEA/H/C/005468) and no new ERA studies have been performed for this updated ERA.

2.2.1. Ecotoxicity/environmental risk assessment

Table 1 Environmental risk assessment – Summary of main study results – Phase I and II

Substance (INN/Invented Name): alpelisib			
CAS-number: 1217486-61-7			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential-log *K*ow	OECD 107 (shake-flask method)	log Dow = 3.04 at pH 5 log Dow = 3.03 at pH 7 log Dow = 3.03 at pH 9	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log Dow = 3.04 at pH 5 log Dow = 3.03 at pH 7 log Dow = 3.03 at pH 9	
	BCF	1.71 L/Kg (low dose) 2.05 L/kg (high dose)	Not B
Persistence	DT50	$DT_{50\ (sediment,\ 12\ ^oC)}$ = 186 d $DT_{50\ (total\ system,\ 12\ ^oC)}$ = 138 d	vP
Toxicity	NOEC or CMR	Reprotoxic	T
PBT-statement:	alpelisib is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	1.5	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = sandy loam Soil 2 = clay Soil 3 = silt loam Sludge 1 = ARA ProRheno Sludge 2 = ARA Birs	OECD 106	$K_{OC,\ soil\ 1}$ = 1'642 L/Kg $K_{OC,\ soil\ 2}$ = 3'873 L/Kg $K_{OC,\ soil\ 3}$ = 1'087 L/Kg $K_{OC,\ sludge\ 1}$ = 263 L/Kg $K_{OC,\ sludge\ 2}$ = 525 L/Kg	
Ready Biodegradability Test	OECD 301B	Not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = sandy loam Sediment 2 = silt loam	OECD 308	$DT_{50, water}$ = 15.8 / 19.7 d $DT_{50, sediment}$ = 186 / 107 d $DT_{50, whole\ system}$ = 138 / 47.4 d shifting to sediment = 48.3 / 39.9% CO_2 = 12.8 / 10.5% NER = 24.2 / 23.3% Transformation products >10% = 2, TP1 = 3.8 / 7.4%, TP2 = 11.5 / 38.6% DT_{50} M1: NA DT_{50} M2: NA	DT50s at 12ºC At day 7 At test end At test end At test tend At test end

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Pseudokirchneriella subcapitata*	OECD 201	EC_{10}	>16'000	µg/L	Growth rate
Daphnia magna, Reproduction Test	OECD 211	EC_{10}	1'600	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	EC_{10}	1'100	µg/L	Growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	Respiration
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	64	mg/kg dw	Emergence ratio and development

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted with this procedure, which was considered acceptable.

According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev.1-Corr.*), the ERA dossier should be updated for type II variations if an increase in environmental exposure is anticipated, such as through a new indication. The MAH has submitted an updated ERA, in which the environmental data generated for the initial Piqray MAA, have been used. In addition, in the more recent Vijoice (alpesilib) procedure, which has been approved on 21 May 2026 (EMEA/H/C/006539), for the treatment of adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy., the ERA was aligned with the current ERA Guideline

(EMEA/CHMP/SWP/4447/00 Rev. 1- Corr). No new environmental studies have been performed. The ERA provided in this document is identical to the submitted ERA in the Vijoice procedure and the use of the highest daily dose and the default F_{pen} is considered acceptable for this application.

The Phase II Tier A dataset includes chronic studies in algae, daphnia and fish, as well as sediment toxicity and a full OECD 305 bioconcentration study. Although alpelisib is persistent in sediment, the bioaccumulation potential is negligible, and therefore the substance does not meet PBT or vPvB criteria. The risk characterisation shows that all PEC/PNEC ratios remain well below 1, with the highest value reported for sediment (0.068). No concerns were identified for surface water, groundwater, sediment organisms, soil, or sewage treatment plant microorganisms.

Based on the ERA submitted in this application, the new/extended indication does not lead to an increase in environmental exposure to alpelisib. No update to the SmPC is required.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated ERA submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of alpelisib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2 Tabular overview of clinical studies

Protocol No., Countries & Study Dates, study status	**Study Design, Purpose & Population Studied**	**Total No., Age Range (mean), Group No.**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
Protocol: CBYL719C2301 Countries: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Republic of Korea, Lebanon, Mexico, Netherlands, Peru, Romania, Russian Federation, Spain, Sweden, Taiwan, Thailand, United Kingdom, United States Start: 23-Jul-2015 End: 09-Jul-2023 Study Status: complete	Design, purpose & population: SOLAR-1: 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	**Total:** 572 **Age:** -PIK3CA mutant cohort (n=341): 25-92 (63.3) years -PIK3CA non-mutant cohort (n=231): 32-88 (62.4) years	• **Form(s):** - alpelisib 50 mg and 200 mg film coated tablets for oral use - placebo matching alpelisib 50 mg and 200 mg film coated tablets - fulvestrant 500 mg intramuscular (i.m.) injection • **Duration:** - *Screening:* 35 days - *Randomized treatment:* no fixed duration; until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment - *Post-treatment follow-up:* Safety follow-up: After discontinuation of study treatment, all patients were followed for safety, AEs and patient reported outcomes (PROs) which were collected until 30 days after last study therapy administration, except in case of death, loss to follow up or withdrawal of consent. Efficacy follow-up: Patients who discontinued treatment for reasons other than disease progression or withdrawal of consent for efficacy follow-up, were continued to be followed every 8 weeks ± 1 week for efficacy during the first 18 months and every 12 weeks ± 1 week until 36 months, then changed to as clinically indicated until

Protocol No., Countries & Study Dates, study status	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
			disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision. <u>Survival follow-up:</u> Patients were followed for survival once they discontinue study treatment and tumor evaluations until the final number of OS events was reached or study had stopped for other reasons
		Groups: 2 (1:1) *PIK3CA mutant cohort*: 341 - alpelsib arm: 169 - placebo arm: 172 *PIK3CA non-mutant cohort*: 231 -alpelsib arm: 115 -placebo arm: 116	**Doses:** alpelisib or placebo 300 mg q.d. orally starting on Cycle 1 Day 1 + fulvestrant 500 mg (i.m.) on Days 1, 15 of Cycle 1 and on Day 1±3 days of each of the subsequent cycles; each cycle was 28 days.

Protocol No., Countries & Study Dates, study status	**Study Design, Purpose & Population Studied**	**Total No., Age Range (mean), Group No.**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
Protocol: CBYL719C2303 Countries: Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Slovakia (Slovak Republic), Spain Start: 29-Nov-2021 End: Ongoing Study Status: ongoing	Design, purpose & population: EPIK-B5: A Phase III, randomized, double-blind, placebo-controlled study of alpelisib (BYL719) in combination with fulvestrant for men, and postmenopausal women, with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor.	Total: 212 (Enrollment complete as of 28-Mar-2025). 188 enrolled as of data cut-off date (15-Oct-2024). Age: 32-84 (61.4) years	• **Form(s):** - alpelisib 50 mg and 200 mg film coated tablets for oral use - placebo matching alpelisib 50 mg and 200 mg film coated tablets - fulvestrant 500 mg ii.m. injection • **Duration:** *Screening*: 28 days Randomized treatment: no fixed duration; until disease Progression per RECIST v1.1 as per BIRC[1] assessment, unacceptable toxicity, start of new antineoplastic therapy, death, lost to follow-up, or withdrawal of consent *Post-treatment follow-up* Safety follow-up: After treatment discontinuation, all participants will enter the safety follow-up which will end 30 days after the participant discontinues from study treatment. Efficacy follow-up: Participants who discontinue study treatment for reasons other than disease progression as assessed by BIRC per RECIST v1.1, death, lost to follow-up or withdrawal of consent/opposition to use data/biological samples will enter efficacy follow-up and will continue tumor assessments until disease progression as assessed by BIRC per RECIST v1.1.

[1] Blinded Independent Review Committee

Protocol No., Countries & Study Dates, study status	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage
			Follow-up post disease progression: For participants who discontinue treatment due to RECIST v1.1 progression as per BIRC assessment and complete the safety follow-up period, PROs will be collected at 8 and 16 weeks post progression. Survival follow-up: Participants will enter the survival follow-up once they complete the safety follow-up period and efficacy follow-up period (if applicable) and be contacted every 12 weeks. Cross-over: Participants randomized to the alpelisib matching placebo plus fulvestrant arm who have disease progression per RECIST v1.1 as assessed by BIRC have the option to be assessed for cross-over to be treated with alpelisib plus fulvestrant
		Groups: 2 (1:1) Arm 1 (alpelisib + fulvestrant): 94 Arm 2 (placebo + fulvestrant): 94	**Doses:** alpelisib or placebo 300 mg q.d. orally starting Cycle 1 Day 1 + fulvestrant 500 mg (i.m.) on Days 1, 15 of Cycle 1 and on Day 1 of each of the subsequent cycles; each cycle is 28 days.

2.3.2. Pharmacokinetics

No new information was generated and submitted in support of this application for the bioavailability / bioequivalence or influence of food on alpelisib exposure.

2.3.3. Pharmacodynamics

No new clinical pharmacology data were generated and submitted in support of this application.

2.3.4. PK/PD modelling

No new PK/PD modelling data were submitted in support of this application.

2.3.5. Discussion on clinical pharmacology

No new clinical pharmacology data were submitted, which was considered acceptable considering that the clinical pharmacology of alpelisib has been established at the currently approved dosage with supporting data in the original MAA (EMEA/H/C/004804/0000).

2.3.6. Conclusions on clinical pharmacology

No new clinical pharmacology data were submitted, which was considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

With this submission the MAH did not present any dose-response study. The dose and posology used in this study were the same as the ones already approved (Procedure No. EMEA/H/C/004804/0000).

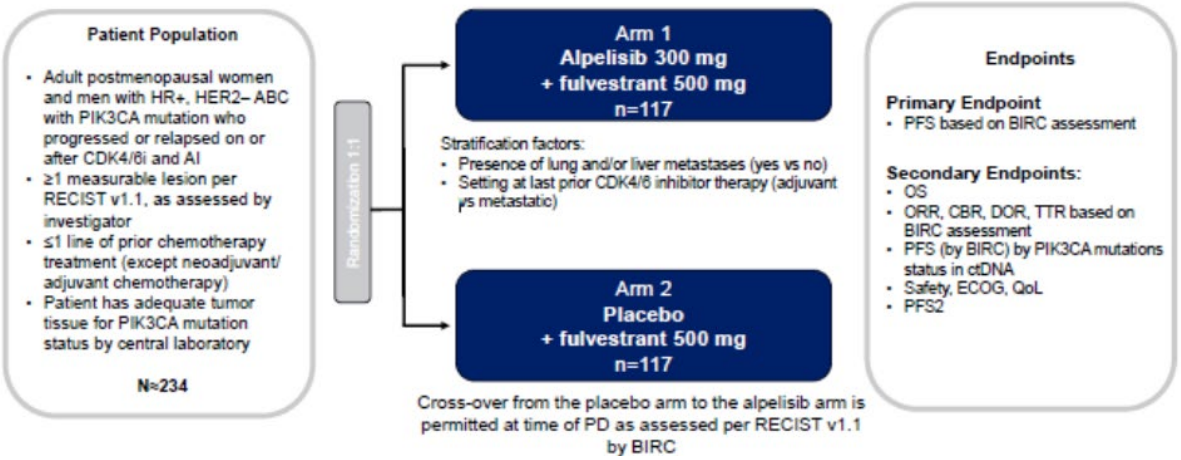
2.4.2. Main study(ies)

Study C2303 (EPIK-B5): a phase III, randomized, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor

Methods

Study C2303 is a phase III, randomized, international, multicenter, double-blind, placebo-controlled trial to assess the efficacy and safety of alpelisib in combination with fulvestrant compared with placebo plus fulvestrant in postmenopausal women, and men with hormone receptor-positive, HER2-negative advanced breast cancer with a PIK3CA mutation who progressed or relapsed on or after treatment with AI and a CDK4/6 inhibitor.

Figure 1 Flowchart of Study C2303 design



Study participants

Inclusion criteria

The main inclusion criteria were, a participant with / may be:

- Adult, ≥ 18 years old at the time of informed consent.
- with advanced (loco regionally recurrent not amenable to curative therapy) or metastatic breast cancer.
- a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory.
- HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC was 2+, a negative in situ hybridization (FISH, CISH, or SISH) test was required by local laboratory testing.
- at least one measurable lesion as per RECIST v1.1 criteria as assessed by the investigator (a lesion at a previously irradiated site was counted as a target lesion only if there was clear sign of progression since the irradiation).
- Relapsed with documented evidence of progression while on (neo)-adjuvant endocrine/endocrine-based therapy or within 12 months from completion of (neo)-adjuvant endocrine/endocrine-based therapy with no treatment for metastatic disease
- Relapsed with documented evidence of progression more than 12 months from completion of (neo) adjuvant endocrine/endocrine-based therapy and then subsequently progressed with documented evidence of progression while on or after only one line of endocrine/endocrine-based therapy for metastatic disease
- Newly diagnosed advanced breast cancer, then relapsed with documented evidence of progression while on or after only one line of endocrine/endocrine-based therapy.

Note: i) Participants with newly diagnosed endocrine treatment naïve advanced breast cancer, ii) Participant who relapsed with documented evidence of progression on/or within 12 months from completion of adjuvant endocrine/endocrine-based therapy and then subsequently relapsed with documented evidence of progression after one line of endocrine/endocrine-based therapy (with either an antiestrogen or an AI) for metastatic disease will NOT be included in the study.

- recurrence or progression of disease during or after combined AI (i.e. letrozole, anastrozole, exemestane) and CDK4/6 inhibitor therapy. The combined AI and CDK4/6 inhibitor therapy was not required to be the latest treatment regimen (including adjuvant setting).
- received ≤ 2 prior lines of systemic therapies overall in the metastatic setting, of which a maximum of 1 line of prior treatment with chemotherapy (except for neoadjuvant / adjuvant chemotherapy) was permitted.
- The presence of PIK3CA mutation(s) determined in tumor tissue prior to enrollment either by a Novartis designated laboratory or in tumor tissue or plasma ctDNA by a local laboratory using an FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN Therascreen® PIK3CA RGQ PCR test.
- adequate tumor tissue for the analysis of PIK3CA mutational status by a Novartis designated laboratory. One new or recent biopsy (collected at screening if feasible) or archival tumor block or slides (15 slides minimum from a surgical specimen, 20 slides minimum from a biopsy) must be provided. It is recommended to provide a tumor sample collected after the most recent progression or recurrence.
- If female, then she had to be in a postmenopausal status.
- an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

Exclusion criteria

The main exclusion criteria were, a participant with / may be:

- symptomatic visceral disease or any disease burden that made the participant ineligible for ET per the investigator's best judgment.
- relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine/endocrine-based therapy with no treatment for metastatic disease.
- inflammatory breast cancer at screening.
- an established diagnosis of diabetes mellitus type I or not controlled type II (based on FPG and HbA1c).
- Child Pugh score B or C.
- currently documented pneumonitis/interstitial lung disease (the chest CT scan performed before start of study treatment for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
- a history of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
- unresolved osteonecrosis of the jaw.
- central nervous system (CNS) involvement which was not previously treated and not fulfilling the following 3 criteria to be eligible for the study: completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study entry and CNS tumor is clinically stable at the time of screening and participant is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
- received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).

- currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
- received prior treatment with fulvestrant, any oral SERDs, any PI3K, mTOR or AKT inhibitor.
- received prior treatment with fulvestrant, any oral selective estrogen receptor degrader (SERD), any Phosphatidylinositol-3-Kinase (PI3K), mammalian Target of Rapamycin (mTOR) or Protein Kinase B (AKT) inhibitor.

Determination of PIK3CA mutation status

Molecular pre-screening period began upon the signature of the Molecular Pre-Screening ICF by the study participant. During this period, the participant's PIK3CA mutation status was evaluated in one of the following ways:

- Participants with a local PIK3CA test result from an FDA-approved PIK3CA CDx test or the CE-IVD QIAGEN Therascreen PIK3CA RGQ PCR test were not required to have their tumor tested centrally to evaluate the PIK3CA mutation status.
- Participants with an unknown PIK3CA mutation status or those with a local PIK3CA test result from a local laboratory using a test which is not approved per protocol (i.e. a test other than an FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN Therascreen PIK3CA RGQ PCR) were required to have their tumor tested centrally to determine the PIK3CA mutation status.

In addition, a blood sample for ctDNA analysis for secondary endpoint was collected. All assessments of samples collected specifically for this study were performed by a Novartis designated laboratory.

Treatments

- Alpelisib + fulvestrant arm: alpelisib 300 mg once daily orally continuously from Cycle 1 Day 1 plus 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).
- Placebo + fulvestrant arm: alpelisib matching placebo 300 mg orally once daily continuously from Cycle 1 Day 1 plus 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: until disease progression based on blinded independent review committee (BIRC) assessment and using RECIST v1.1, unacceptable toxicity, or discontinuation from the study treatment for any other reason.

Objectives and estimands

Primary objective and related endpoint(s)

Table 3 Primary objective and related endpoint(s)

Primary objective	Endpoint for primary objective
• To determine whether treatment with alpelisib plus fulvestrant prolongs PFS	• PFS based on BIRC assessment and using RECIST v1.1 criteria

compared to treatment with placebo plus fulvestrant	

Secondary objectives and related endpoints

Table 4 Primary objective and related endpoint(s)

Secondary objectives	Endpoints for secondary objectives
• To determine whether treatment with alpelisib plus fulvestrant prolongs OS compared to treatment with placebo plus fulvestrant	• Overall survival
• To evaluate alpelisib plus fulvestrant compared to placebo plus fulvestrant, with regards to objective response by RECIST v1.1 criteria	• Overall response rate with confirmed response, CBR with confirmed response, DOR with confirmed response, and TTR based on BIRC assessment and RECIST v1.1.
• To evaluate the association between PIK3CA mutation status as measured in ctDNA at baseline with PFS upon treatment with alpelisib	• PFS based on BIRC assessment and using RECIST v1.1 criteria for participants by PIK3CA mutation status assessed in ctDNA at baseline.
• To assess safety and tolerability of alpelisib in combination with fulvestrant compared to placebo in combination with fulvestrant	• Incidence, type and severity of adverse events per CTCAE v4.03 criteria including changes in laboratory values, vital signs, hepatic, renal and cardiac assessments. Tolerability: dose interruptions, reductions, dose intensity and duration of exposure for all drug components
• To evaluate treatment with alpelisib plus fulvestrant compared to placebo plus fulvestrant, with respect to time to deterioration of ECOG performance status	• Time to definitive deterioration of ECOG performance status from baseline
• To evaluate patient-reported outcomes of alpelisib plus fulvestrant compared to placebo and fulvestrant.	• Time to definitive (10%) deterioration in the global health status/QoL and symptom scale scores of the EORTC QLQ-C30 Change from baseline in global health status/QoL and symptom scale scores of the EORTC QLQ-C30
• To explore the long-term benefit intermediate to PFS and OS	• Time from randomization to objective tumor progression on next line treatment or death from any cause (PFS2)

Exploratory objectives

Table 5 Primary objective and related endpoint(s)

Exploratory objectives	Endpoints for exploratory objectives
• To assess molecular alterations associated with resistance to prior treatment with CDK4/6 inhibitors	• Gene expression or genetic alteration analysis in tumor tissue and/or ctDNA collected prior to study treatment and association with clinical efficacy endpoint (such as PFS, OS)

• To explore potential role of ctDNA as surrogate endpoint for monitoring disease progression and understanding acquired resistance mechanisms to study treatment	• Molecular analysis of ctDNA samples collected prior to study treatment and at the disease progression and its correlation with clinical efficacy
• To explore patient-reported QoL and pain	• Change from baseline in the overall health status of the EQ 5D-5L index score and VAS. Change from baseline in the worst pain item of BPI-SF
• To explore whether treatment with alpelisib plus fulvestrant delays start of chemotherapy following documented progression	• Time to start of first subsequent chemotherapy

Sample size

Based on data for participants whose HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, progressed on or after AI plus CDK4/6 inhibitor-based treatment from Study C2301 (SOLAR-1), Cohort A of Study X2402, as well as real world evidence data retrieved from the Flatiron CGDB, the median PFS in the control arm in participants that progressed on or after AI plus CDK4/6 inhibitor based treatment was assumed to be 5 months for the purpose of sample size calculation.

It was expected that treatment with alpelisib + fulvestrant will result in a 40% reduction in the hazard rate, i.e. an expected hazard ratio of 0.6 (corresponding to an increase in median PFS to 8.3 months under the exponential model assumption).

In order to ensure 90% power to test the null hypothesis: PFS hazard ratio=1 versus the specific alternative hypothesis: PFS hazard ratio 0.6, it was calculated that a total of 165 events needed to be observed. This calculation assumed analysis by a one-sided log-rank test at the overall 2.5% level of significance, and participants randomized to the two treatment arms in a 1:1 ratio and a two-look group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function using information fractions of (0.8, 1).

Based on 234 participants and assuming an enrolment rate of 3 participants during the first 6 months, 6 participants up to 12 months, 8 participants afterwards, and a rate of losses to follow up for PFS of about 5% at the time of the analysis, it was estimated that these 165 PFS events will be observed approximately 36 months after the randomization date of the first participant.

Randomisation

Participants were randomized to either alpelisib plus fulvestrant or alpelisib-matching placebo plus fulvestrant following a 1:1 randomization ratio and stratified by presence of lung and/or liver metastases (yes vs. no) and setting at last prior CDK4/6 inhibitor therapy (adjuvant vs metastatic).

Blinding (masking)

This was a participant, investigator, and sponsor-blinded study. Participants, investigator staff, persons performing the assessments, blinded independent review committee (BIRC), local radiologists, and the Novartis Clinical Trial Team (CTT) were to remain blinded to the identity of the treatment from the time of randomization as defined below.

The following methods will be used to maintain the blind:

(1) Randomisation data kept strictly confidential until the time of database lock for the primary PFS analysis.

(2) the identity of the treatments concealed by the use of study treatment that were all identical in packaging, labelling, schedule of administration, appearance, taste, and odor. Unblinding a single participant at a site was permitted after disease progression confirmed by BIRC upon investigator request to determine eligibility for cross-over to treatment with alpelisib plus fulvestrant. Unblinding a single participant for safety reasons (necessary for participant management) could occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

Participants randomized to the alpelisib-matching placebo plus fulvestrant arm who have disease progression per RECIST v1.1 as assessed by BIRC had the option to crossover to be treated with alpelisib plus fulvestrant.

Cross-over

Unblinding a single participant at a site was permitted after disease progression confirmed by BIRC after discussion with the Novartis team to determine eligibility for cross-over to treatment with alpelisib plus fulvestrant.

For participants who crossed-over, PROs had to be collected before first administration of alpelisib plus fulvestrant.

Statistical methods

Estimand for the primary endpoint

Progression-free survival	
Population	All participants randomised with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after AI plus CDK4/6 inhibitor-based treatment.
Treatment condition	The investigational treatment is alpelisib in combination with fulvestrant plus any subsequent anti-neoplastic therapy as needed. The control treatment is alpelisib-matching placebo in combination with fulvestrant plus any subsequent antineoplastic therapy as needed.
Endpoint (variable)	PFS based on BIRC assessment and using RECIST v1.1 criteria.
Population-level summary	PFS hazard ratio (alpelisib plus fulvestrant versus alpelisib-matching placebo plus fulvestrant) and its 95% confidence interval.
Intercurrent events and strategy to handle them	
Discontinuation of study treatment for any reason	PFS events collected after discontinuation of study treatment will be used for the primary analysis (treatment policy strategy).

Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 were not to be considered as disease progression for PFS derivation. Clinical deterioration without objective radiological evidence were not to be considered as documented disease progression.

Handling of missing values not related to intercurrent events

In the primary analysis, PFS was censored at the date of the last adequate tumor assessment if no PFS event per BIRC was observed prior to the analysis cut-off date.

If a PFS event was observed after one or more missing or non-adequate tumor assessments, the actual date of event was used.

Censoring rules for PFS analysis

Table 6 Outcome and event/censor dates for PFS analysis

Situation		**Options for end-date (progression or censoring)[1]** **(1) = default unless specified differently in the protocol or RAP**	**Outcome**
A	No baseline assessment	(1) Date of randomisation / start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment[2]	Censored

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
E	Treatment discontinuation due to 'Disease progression' without documented progression i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of the last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1 = Definitions can be found in section 3.2.7 of CSR

2 = After the last adequate tumour assessment. 'Date of next scheduled assessment' is defined in section 3.2.7 of CSR

3 = The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

Estimand for secondary endpoints

Not applicable. Secondary objectives fell outside of the statistical testing framework specified for the primary objectives thus no statistical testing was undertaken.

Outcome and event/censor dates for OS analysis

The pattern of censored data was toe examined between the treatment groups: reasons for censoring ('Alive' or 'Lost to follow-up') and death cause were to be summarised by treatment group. In addition, survival status, reason for censoring and death cause were to be listed.

Interim analysis

One interim analysis (IA) of PFS by BIRC was planned after approximately 132/165 PFS events, corresponding to an 80% information fraction, to allow early declaration of superior efficacy if the prespecified boundary was crossed. The actual IA, performed at the 15-Oct-2024 data cut-off, included 141 PFS events, corresponding to an 85% information fraction, and was conducted in the 188 participants randomised at that time while enrolment was still ongoing. Because the actual number of events differed from the planned 132, the efficacy boundary was recalculated using the prespecified Lan-DeMets alpha-spending function. It has been clarified that this IA constituted the primary analysis.

The IA was performed by an independent statistician and reviewed by the DMC. Based on the efficacy and safety data from the 188 participants, the DMC recommended permanent discontinuation of enrolment on 28-Mar-2025. By then, 212 of the planned 234 participants had been enrolled. Therefore, the primary analysis was based on 188 participants, while the final analysis was based on 212 participants

Sensitivity analyses for primary endpoint/estimand

As a sensitivity analysis, PFS as per local review was analysed using a stratified Cox model, with the same analysis conventions as the primary efficacy analysis, and the treatment effect was summarised by the HR with its 95% CI. Kaplan-Meier curves, medians and 95% CIs of the medians were presented for each treatment group.

In addition, the HR and 95% CI for PFS as per BIRC were also obtained from an unstratified Cox model.

Furthermore, the HR and 95% CI for PFS as per BIRC were also obtained from a stratified Cox model with stratification factors derived from the clinical database, in case at least 5% of the participants had discrepancies between strata at randomization (using interactive response technology (IRT) data) and strata derived from the eCRF data. This analysis also included Kaplan-Meier median with its 95% CI.

Supplemental analyses methods for PFS

As supplementary analyses, subgroup analyses were performed on each level of randomisation stratification factors. If the primary analysis was statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics was performed.

A multivariate Cox regression model stratified by randomisation stratification factors (per IRT) was fitted to evaluate the effect of other baseline demographic and disease characteristics on the estimated hazard ratio.

Number of participants and number of events by treatment group within each stratum (per IRT) were presented along with the hazard ratio for treatment effect obtained using unstratified Cox proportional hazards regression models with corresponding confidence intervals.

Results

Participant flow

Figure 2 Study C2303 participant flow

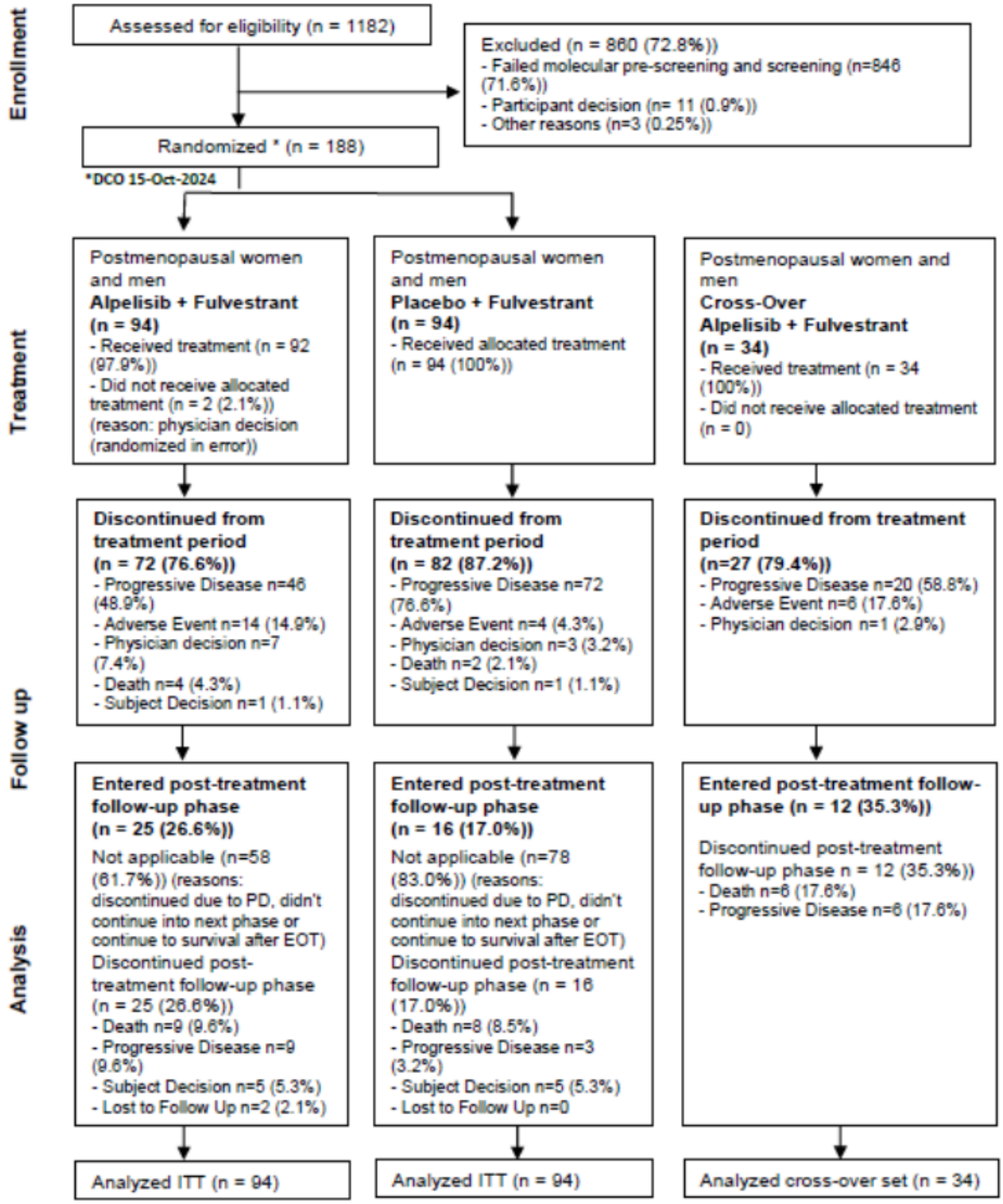


Table 7 Participant disposition (Full Analysis Set, Double-blind treatment period)

Disposition/Reason	Alpelisib + Fulvestrant N =94 n (%)	Placebo + Fulvestrant N =94 n (%)	Total N =188 n (%)
Participants randomized			
Treated	92 (97.9)	94 (100)	186 (98.9)
Not treated	2 (2.1)	0	2 (1.1)
Reason for not being treated			
Physician Decision	2 (2.1)	0	2 (1.1)
Treatment ongoing*	20 (21.3)	12 (12.8)	32 (17.0)
End of treatment	72 (76.6)	82 (87.2)	154 (81.9)
Primary reason for end of treatment			
Progressive Disease	46 (48.9)	72 (76.6)	118 (62.8)
Adverse Event	14 (14.9)	4 (4.3)	18 (9.6)
Physician Decision	7 (7.4)	3 (3.2)	10 (5.3)
Death	4 (4.3)	2 (2.1)	6 (3.2)
Subject Decision	1 (1.1)	1 (1.1)	2 (1.1)
Post Treatment follow-up Phase			
Participants entered post treatment follow-up phase	25 (26.6)	16 (17.0)	41 (21.8)
Not Applicable^	58 (61.7)	78 (83.0)	136 (72.3)
Participants discontinued from post treatment follow-up phase	25 (26.6)	16 (17.0)	41 (21.8)
Primary reason for post treatment follow-up discontinuation			
Death	9 (9.6)	8 (8.5)	17 (9.0)
Progressive Disease	9 (9.6)	3 (3.2)	12 (6.4)
Subject Decision	5 (5.3)	5 (5.3)	10 (5.3)
Lost To Follow-Up	2 (2.1)	0	2 (1.1)
Survival follow-up Phase			
Participants entered survival follow-up phase	53 (56.4)	56 (59.6)	109 (58.0)

* Participants ongoing at the time of the cut-off 15OCT2024
^Participants 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
- Percentage is based on N
- Reason for not being treated is from CRF completion page

Table 8 Participant disposition (Cross-over Set, Cross-over Period)

Disposition/Reason	Open-label Alpelisib + Fulvestrant N =34 n(%)
Subjects treated	
Treated	34 (100)
Not Treated	0
Reason for not being treated	
Treatment Ongoing #	7 (20.6)
End of Treatment	27 (79.4)
Primary reason for end of treatment	
Progressive Disease	20 (58.8)
Adverse Event	6 (17.6)
Physician Decision	1 (2.9)
Post Treatment follow-up Phase	
Participiants entered post-treatment follow-up phase	12 (35.3)
Participants discontinued from post treatment follow-up phase	12 (35.3)
Primary reason for post treatment follow-up discontinuation	
Death	6 (17.6)
Progressive Disease	6 (17.6)
Survival follow-up Phase	
Participants entered in the Survival follow-up phase	25 (73.5)

Participants ongoing at the time of the cut-off 15OCT2024

Recruitment

First patient first visit – molecular pre-screening): 29-Nov-2021

First patient first visit – screening: 17-Dec-2021

Data cut-off (DCO): 15-Oct-2024. Ongoing.

The study was initiated in 97 sites, out of which 93 pre-screened at least one patient and 69 randomized at least one patient. These sites were located in 17 countries (Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Slovak Republic, Spain).

Conduct of the study

Protocol amendments

Table 9 List of protocol amendments, effective dates and summary of protocol amendments

Document & Effective date	Summary of key changes
Original Protocol, 24-Jun-2021	
Amended Protocol Version 01, 10-May-2022	• Allowance of enrollment of participants with tumors harboring a PIK3CA mutation based on local testing results (if testing performed using an FDA-approved PIK3CA CDx for alpelisib or the CE-IVD QIAGEN Therascreen® PIK3CA RGQ PCR test). • Option (strongly recommended) to perform exploratory pre-dose biomarker collection of tumor biopsies after a participant had progressed on a CDK4/6 inhibitor. • Clarification of some inclusion/exclusion criteria (no prior oral SERD treatment allowed, no more than 2 prior lines of systemic therapies allowed, and update of the maximum limit of QTcF was updated to align). • Included additional guidance to optimise AE management (incl. use of metformin XR for better glucose management and addition of management guidelines for HHNKS, DKA, diarrhea, colitis, and hypersensitivity reactions).
Amended Protocol Version 02, 16-Feb-2023	• Update of inclusion criterion (modification of key laboratory parameters and clarification of the assessment of adequate bone marrow and organ function). • Revision of the measurable disease per RECIST v1.1 at baseline criteria confirmation (investigator's assessment prior to randomization). • Allowance of molecular pre-screening and main screening simultaneously, if needed. • Update of hyperglycemia management recommendation to consider prophylactic metformin before initiating alpelisib treatment.
Amended Protocol Version 03, 08-Aug-2023	• Introduction of an efficacy interim analysis at approximately 80% of BIRC PFS events planned at the final analysis. The Lan-DeMets alpha spending function with O'Brien-Fleming boundary was proposed to construct the efficacy stopping boundaries. The primary intent and rationale for adding this interim analysis was to allow an early confirmation of the efficacy results observed in study CBYL719C2301 (SOLAR-1), should the data meet the interim efficacy boundary.

	Changes compared to the previous version (Protocol amendment 3; dated 08-Aug-2023): "162" events triggering the final analysis has been changed to "165" events to trigger the final analysis, participant enrollment rate updated after 8 months; estimate for when required PFS events will be observed updated to 36 months.
Amended Protocol Version 04, 22-Oct-2024[1]	• Updated liver safety guidance focusing on monitoring using Hy's Law criteria and report any Hy's Law cases as SUSARs • Clarification with regards to collect biopsies in cases of skin toxicity grade 3 and 4.

1. Amended Protocol Version 04 was planned to be implemented on 14-Oct-2024, while it was finally implemented ("release date") on 22-Oct-2024.

Protocol deviations

Double-blind period: The proportion of participants with at least one protocol deviation was of 59.6% in the alpelisib + fulvestrant arm and 52.1% in the placebo + fulvestrant arm. The most common protocol deviation (reported in ≥10% of participants in any arm) was due to any significant GCP violation (e.g. trial assessments continuously not conducted despite re-training) (alpelisib + fulvestrant arm: 10.6% and placebo + fulvestrant arm: 12.8%).

Cross-over period: The most common protocol deviation (reported in ≥5% of participants) was due to central laboratory results related to participant eligibility were not available (not received/not done) (5.9%), participant did not withdraw consent, lost to follow-up or died, but safety/survival follow-up period was not appropriately followed up (5.9%), concurrent treatment with prohibited drugs as per protocol which put participants under significant risk (5.9%).

Baseline data

Demographic baseline characteristics

Table 10 Demographics and baseline characteristics (Full Analysis Set, Double-blind treatment period)

Demographic variable	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)	All Participants N=188 n (%)
Age group -n (%)			
<65 years	53 (56.4)	58 (61.7)	111 (59.0)
≥65 years	41 (43.6)	36 (38.3)	77 (41.0)
Age (years)			
n	94	94	188
Mean (SD)	61.9 (10.30)	60.8 (10.84)	61.4 (10.56)
Median	62.0	61.5	62.0
Q1-Q3	56.0 - 69.0	54.0-68.0	54.5 - 69.0
Min-Max	35.0 - 80.0	32.0-84.0	32.0 - 84.0
Sex -n (%)			
Female	94 (100)	92 (97.9)	186 (98.9)
Male	0	2 (2.1)	2 (1.1)
Race -n (%)			

White	86 (91.5)	83 (88.3)	169 (89.9)
Unknown	7 (7.4)	11 (11.7)	18 (9.6)
Asian	1 (1.1)	0	1 (0.5)
Ethnicity -n (%)			
Not Hispanic or Latino	74 (78.7)	66 (70.2)	140 (74.5)
Not reported	15 (16.0)	20 (21.3)	35 (18.6)
Hispanic or Latino	2 (2.1)	5 (5.3)	7 (3.7)
Unknown	2 (2.1)	3 (3.2)	5 (2.7)
Missing	1 (1.1)	0	1 (0.5)
ECOG performance status -n (%)			
0	53 (56.4)	60 (63.8)	113 (60.1)
1	39 (41.5)	33 (35.1)	72 (38.3)
2	0	1 (1.1)	1 (0.5)
Missing	2 (2.1)	0	2 (1.1)
Weight (kg)			
n	92	94	186
Mean (SD)	68.3 (14.74)	68.9 (13.73)	68.6 (14.20)
Median	64.5	68.0	67.0
Q1-Q3	58.2 - 76.1	60.0-75.0	59.0-76.0
Min-Max	46 - 114	38.1-107.0	38.1-114.0
Height (cm)			
n	92	94	186
Mean (SD)	161.9 (5.75)	162.0 (7.18)	161.9 (6.50)
Median	163.0	162.0	162.0
Q1-Q3	158.0-165.8	156.0-167.0	158.0-166.0
Min-Max	146.0-173.0	147.0-180.0	146.0-180.0
Body mass index (kg/m^2)			
n	92	94	186
Mean (SD)	26.1 (5.65)	26.3 (4.95)	26.2 (5.29)
Median	25.0	25.5	25.2
Q1-Q3	22.8-28.7	22.8-28.9	22.8-28.9
Min-Max	16.9-50.7	14.0-39.5	14.0-50.7

Body Mass Index: BMI (kg/m^2) = weight(kg)/(height(m)**2)

Cross-over period: the median age was 61.0 years (range: 32.0-79.0). The participant population was primarily composed of women (33 [97.1%] participants), with 1 (2.9%) man. The majority of participants were White (94.1%). All participants had an ECOG performance status of 0 or 1 (ECOG 0: 61.8% and ECOG 1: 38.2%).

Baseline disease characteristics

Table 11 Diagnosis and extent of cancer (Full Analysis Set, Double-blind treatment period)

Disease history	Alpelisib + Fulvestrant N=94	Placebo + Fulvestrant N=94	All Participants N=188
Primary site of cancer-n (%)			
Breast	93 (98.9)	94 (100)	187 (99.5)
Predominant histology/cytology-n (%)			
Invasive ductal carcinoma	53 (56.4)	49 (52.1)	102 (54.3)
Invasive lobular carcinoma	18 (19.1)	13 (13.8)	31 (16.5)
In situ carcinoma	1 (1.1)	1 (1.1)	2 (1.1)
Adenocarcinoma	9 (9.6)	11 (11.7)	20 (10.6)
Lobular carcinoma in situ	2 (2.1)	0	2 (1.1)
Papillary	0	2 (2.1)	2 (1.1)
Ductual carcinoma in situ (DCIS)	1 (1.1)	5 (5.3)	6 (3.2)
Undifferentiated carcinoma	0	1 (1.1)	1 (0.5)
Inflammatory carcinoma	0	1 (1.1)	1 (0.5)
Other	8 (8.5)	10 (10.6)	18 (9.6)
Not applicable	1 (1.1)	1 (1.1)	2 (1.1)
Histologic grade-n (%)			
Well differentiated	9 (9.6)	16 (17.0)	25 (13.3)
Moderately differentiated	41 (43.6)	40 (42.6)	81 (43.1)
Poorly differentiated	21 (22.3)	21 (22.3)	42 (22.3)
Undifferentiated	2 (2.1)	3 (3.2)	5 (2.7)

Unknown [1]	20 (21.3)	14 (14.9)	34 (18.1)
Stage at initial diagnosis-n (%)			
0	1 (1.1)	1 (1.1)	2 (1.1)
I	4 (4.3)	5 (5.3)	9 (4.8)
IA	6 (6.4)	3 (3.2)	9 (4.8)
IB	1 (1.1)	3 (3.2)	4 (2.1)
IC	1 (1.1)	0	1 (0.5)
II	4 (4.3)	6 (6.4)	10 (5.3)
IIA	18 (19.1)	19 (20.2)	37 (19.7)
IIB	2 (2.1)	10 (10.6)	12 (6.4)
III	2 (2.1)	0	2 (1.1)
IIIA	6 (6.4)	5 (5.3)	11 (5.9)
IIIB	2 (2.1)	1 (1.1)	3 (1.6)
IIIC	2 (2.1)	1 (1.1)	3 (1.6)
IV	40 (42.6)	38 (40.4)	78 (41.5)
IVA	1 (1.1)	0	1 (0.5)
IVB	2 (2.1)	0	2 (1.1)
Missing	1 (1.1)	2 (2.1)	3 (1.6)
Stage at time of study entry-n (%)			
II	1 (1.1)	0	1 (0.5)
IV	88 (93.6)	89 (94.7)	177 (94.1)
IVA	1 (1.1)	3 (3.2)	4 (2.1)
IVB	3 (3.2)	2 (2.1)	5 (2.7)
Time since initial diagnosis of primary site (months)-n (%)			
n	93	94	187
<6 months	2 (2.1)	0	2 (1.1)
≥6 months	90 (95.7)	94 (100)	184 (97.9)
Unknown	1 (1.1)	0	1 (0.5)
Time since initial diagnosis of primary site (months)			
n	92	94	186
Mean	97.1	99.4	98.3
SD	90.68	84.87	87.56
Median	57.0	67.5	60.5
Minimum	5.7	8.7	5.7
Maximum	370.4	372.2	372.2
Time from initial diagnosis to first recurrence/progression (months)			
n	93	94	187
Mean	67.7	78.1	72.9
SD	70.84	72.91	71.88

Median	36.0	48.3	40.2
Minimum	0.0	0.0	0.0
Maximum	327.5	365.6	365.6
Time since most recent relapse/ progression (months) - if last treatment was for advanced disease-n (%)			
n	91	90	181
>3 months	13 (13.8)	15 (16.0)	28 (14.9)
1-≤3 months	67 (71.3)	66 (70.2)	133 (70.7)
<1 month	11 (11.7)	9 (9.6)	20 (10.6)
Time since most recent relapse/ progression (months) - if last treatment was for advanced disease			
n	91	90	181
Mean	2.3	2.1	2.2
SD	2.03	1.11	1.64
Median	1.9	1.8	1.9
Minimum	0.5	0.5	0.5
Maximum	15.0	6.9	15.0
Types of lesions at baseline-n (%)			
Both target and non-target	92 (97.9)	94 (100)	186 (98.9)
Unknown	1 (1.1)	0	1 (0.5)
Current extent of disease (metastatic sites)-n (%)			
n	93	94	187
CNS	1 (1.1)	2 (2.1)	3 (1.6)
Bone	77 (81.9)	78 (83.0)	155 (82.4)
Bone only	6 (6.4)	15 (16.0)	21 (11.2)
Visceral	74 (78.7)	72 (76.6)	146 (77.7)
Liver	51 (54.3)	49 (52.1)	100 (53.2)
Lung	38 (40.4)	36 (38.3)	74 (39.4)
Other visceral	8 (8.5)	2 (2.1)	10 (5.3)
Skin	6 (6.4)	5 (5.3)	11 (5.9)
Lymph nodes	34 (36.2)	32 (34.0)	66 (35.1)
Other	1 (1.1)	0	1 (0.5)
Number of metastatic sites-n (%)			
n	93	94	187
1	15 (16.0)	22 (23.4)	37 (19.7)
2	43 (45.7)	40 (42.6)	83 (44.1)
3	28 (29.8)	26 (27.7)	54 (28.7)
4	4 (4.3)	6 (6.4)	10 (5.3)
≥5	3 (3.2)	0	3 (1.6)
HER2 receptor status-n (%)			
n	93	94	187
Negative	93 (98.9)	94 (100)	187 (99.5)
Estrogen receptor status-n (%)			
n	93	94	187
Positive	93 (98.9)	94 (100)	187 (99.5)
Progesterone receptor status-n (%)			
n	93	94	187
Positive	67 (71.3)	79 (84.0)	146 (77.7)
Negative	25 (26.6)	14 (14.9)	39 (20.7)
Unknown	1 (1.1)	1 (1.1)	2 (1.1)
Estrogen and/or progesterone receptor status-n (%)			
n	93	94	187
At least one positive	93 (98.9)	94 (100)	187 (99.5)
Both positive	67 (71.3)	79 (84.0)	146 (77.7)

1 includes participants with histological grade performed with unknown result

All patients had advanced breast cancer with a PIK3CA mutation and had received prior treatment with an aromatase inhibitor and a CDK4/6 inhibitor. Ninety-three (98.9%) patients received their last prior CDK4/6 inhibitor therapy in the metastatic setting, while 1 (1.1%) patient received it in the adjuvant setting. Letrozole was the most commonly used aromatase inhibitor, and ribociclib and palbociclib the

most commonly used CDK4/6 inhibitors. The setting of last endocrine therapy prior to study enrolment was metastatic in 97.3% of subjects and adjuvant therapy in 9.6% of subjects. Overall, 83.5% of the patients were considered to have endocrine-resistant disease; primary endocrine resistance (*de novo* resistance) was observed in 6.9% and secondary endocrine resistance (relapse/progression following an initial response) in 76.6% of patients. In the metastatic setting prior chemotherapy treatment had been received by 12.8% and 18.1% of patients in the alpelisib plus fulvestrant arm and in the placebo plus fulvestrant arm, respectively.

Cross-over period: most participants had stage IV cancer at initial diagnosis (41.2%), while 94.1% of participants had stage IV disease at the time of study entry. The predominant histology/cytology was invasive ductal carcinoma (55.9%). The majority of participants had moderately differentiated tumors (61.8%), but 23.5% of participants had poorly differentiated tumors. Most participants had 2 metastatic sites (44.1%) of disease. Lung metastasis was reported in 29.4% of participants.

Numbers analysed

The primary analysis at the interim data cut-off (15-Oct- 2024) was conducted with the available 188 participants while enrolment was ongoing. The DMC reviewed the interim analysis efficacy and safety data based on those 188 participants and recommended to permanently stop the enrolment on 28-Mar-2025, with a total of 212 participants on the 234 planned to be enrolled. Thus, the IA (i.e., the primary analysis) was based on 188 patients, and the final analysis was based on 212 patients.

Table 12 Analysis set by treatment and stratum

Analysis set	Alpelisib + Fulvestrant N =94 n (%)	Placebo + Fulvestrant N =94 n (%)	Open-label Alpelisib + Fulvestrant N=34 N (%)
Full Analysis Set	94 (100)	94 (100)	
Lung And/Or Liver Metastases: Absent	27 (28.7)	27 (28.7)	
Lung And/Or Liver Metastases: Present	67 (71.3)	67 (71.3)	
Setting At Last Prior Cdk4/6 Inhibitor Therapy: Adjuvant	1 (1.1)	1 (1.1)	
Setting At Last Prior Cdk4/6 Inhibitor Therapy: Metastatic	93 (98.9)	93 (98.9)	
Safety Set	92 (97.9)	94 (100)	
Lung And/Or Liver Metastases: Absent	27 (28.7)	27 (28.7)	
Lung And/Or Liver Metastases: Present	65 (69.1)	67 (71.3)	
Setting At Last Prior Cdk4/6 Inhibitor Therapy: Adjuvant	1 (1.1)	1 (1.1)	
Setting At Last Prior Cdk4/6 Inhibitor Therapy: Metastatic	91 (96.8)	93 (98.9)	
Cross-over Set			34 (100)
Lung And/Or Liver Metastases: Absent			6 (17.6)
Lung And/Or Liver Metastases: Present			28 (82.4)
Setting At Last Prior Cdk4/6 Inhibitor Therapy: Metastatic			34 (100)

-N is the number of participants in the Full analysis set.
- Full analysis set includes all participants who were randomized to study treatment.
- Safety set includes all participants who are randomized to study treatment and receive at least one dose of study treatment (either fulvestrant or alpelisib/placebo).
- Cross-over set includes all participants randomized to the alpelisib-matching placebo plus fulvestrant arm who received at least one dose of open-label alpelisib plus fulvestrant after cross-over following confirmed disease progression per BIRC.
- Strata defined by Presence of lung and/or liver metastases, setting at last prior CDK4/6 inhibitor therapy per IRT.

Outcomes and estimation

Primary endpoint

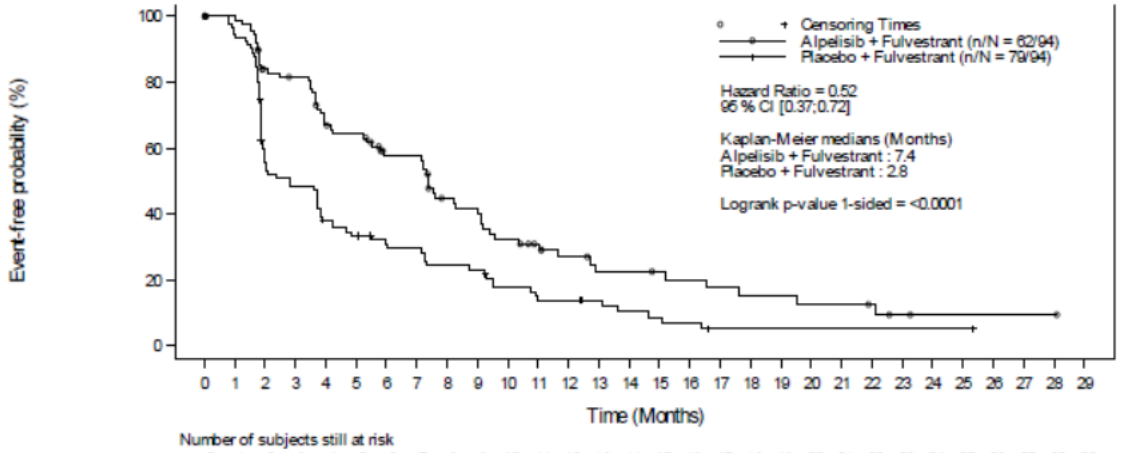
PFS by BIRC assessment (DCO: 15-Oct-2024, primary PFS analysis)

Table 13 Stratified log-rank test and Cox regression model for PFS (months) based on BIRC assessment, comparison of treatment with control – overall and by eCRF stratification factor - Full Analysis Set

	Event/N (%)	Median PFS (95% CI) (months) (3)	p-value (4)	Cox Model Hazard Ratio (5)	95% CI
All participants (1)					
Alpelisib + Fulvestrant	62/94 (66.0)	7.4 (5.52,9.10)	<0.0001	0.52	(0.37,0.72)
Placebo + Fulvestrant	79/94 (84.0)	2.8 (1.94,3.84)			
Adjuvant setting at last prior CDK4/6 inhibitor therapy (2)					
Alpelisib + Fulvestrant	1/1 (100)	1.7 (NE, NE)			
Metastatic setting at last prior CDK4/6 inhibitor therapy (2)					
Alpelisib + Fulvestrant	60/91 (65.9)	7.4 (5.52,9.10)		0.55	(0.39,0.76)
Placebo + Fulvestrant	79/94 (84.0)	2.8 (1.94,3.84)			
Presence of lung/liver metastases (2)					
Alpelisib + Fulvestrant	45/67 (67.2)	7.2 (3.98,7.52)		0.50	(0.34,0.74)
Placebo + Fulvestrant	56/64 (87.5)	2.0 (1.87,3.61)			
Absence of lung/liver metastases (2)					
Alpelisib + Fulvestrant	17/27 (63.0)	9.2 (7.33,17.64)		0.57	(0.30,1.08)
Placebo + Fulvestrant	23/30 (76.7)	6.0 (2.07,9.49)			

(1) Both Log-rank test and Cox PH model are stratified by presence of lung/liver metastases.
(2) Subgroup analysis of stratification factors (per eCRF) uses an unstratified Cox proportional hazards model.
(3) Median (time to event) and its 95% CI are generated by KM estimation.
(4) p-value will only be calculated for 'All participants' group.
(5) Hazard Ratio of Alpelisib + Fulvestrant vs. Placebo + Fulvestrant (Placebo + Fulvestrant is the control).

Figure 3 Kaplan-Meier plot of PFS as per BIRC assessment - Full Analysis Set



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	17	18	19	20	21	22	23	24	25	26	27	28	29
Alpelisib + Fulvestrant	94	88	70	67	54	51	41	41	29	27	21	17	13	10	10	9	8	7	6	6	5	5	4	2	1	1	1	1	1	0
Placebo + Fulvestrant	94	86	49	42	32	28	24	23	19	18	13	10	10	8	6	5	4	1	1	1	1	1	1	1	1	1	0	0	0	0

Stratified Log-rank test and stratified Cox model using strata per IRT defined by (i) Presence of lung and/or liver metastases.

Table 14 Summary of type of events for PFS as per BIRC assessment - Full Analysis Set

	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)
Number of PFS events	62 (66.0)	79 (84.0)
PD	56 (59.6)	70 (74.5)
Death	6 (6.4)	9 (9.6)
Number censored	32 (34.0)	15 (16.0)

Table 15 Reasons for censoring participants in PFS (BIRC assessment) - Full Analysis Set

Study analysis endpoint(s)	Reason of censoring	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)
PFS	Number of subjects censored	32 (34.0)	15 (16.0)
	Reason of censoring		
	Ongoing without event	19 (20.2)	12 (12.8)
	Lost to follow-up	1 (1.1)	0
	Withdrew Consent	4 (4.3)	1 (1.1)
	Adequate assessment no longer available	8 (8.5)	2 (2.1)

Secondary endpoints

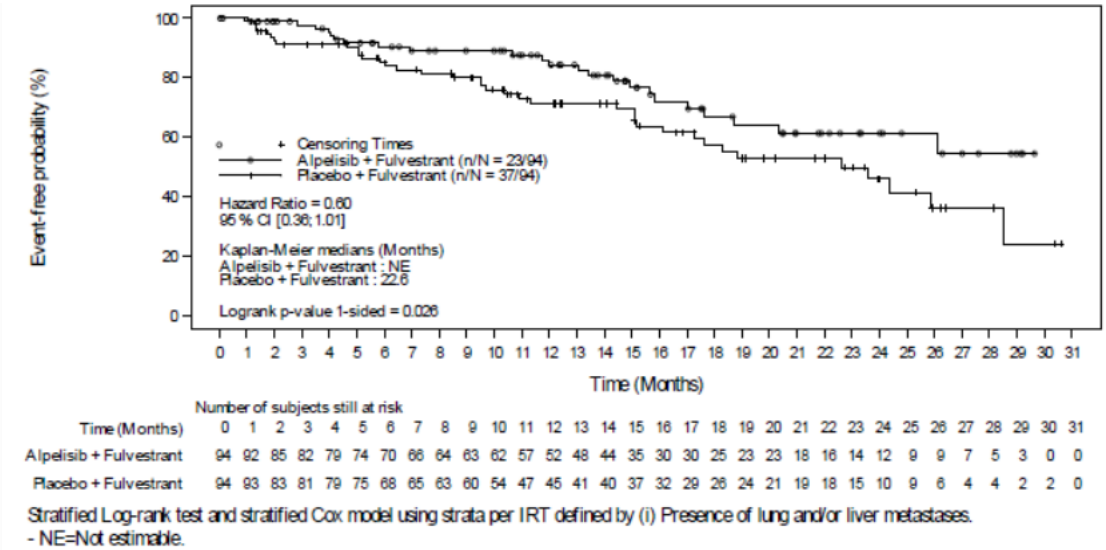
Overall survival (DCO: 15-Oct-2024; IA OS analysis)

Table 16 Stratified log-rank test and Cox regression model for OS (months), comparison of treatment with control –overall and by eCRF stratification factor - Full Analysis Set

	Event/N (%)	Median OS (95% CI) (months) (3)	p-value (4)	Cox Model Hazard Ratio (5)	95% CI
All participants (1)					
Alpelisib + Fulvestrant	23/94 (24.5)	NE (18.69, NE)	0.026	0.60	(0.36,1.01)
Placebo + Fulvestrant	37/94 (39.4)	22.6 (16.10,28.52)			
Adjuvant setting at last prior CDK4/6 inhibitor therapy (2)					
Alpelisib + Fulvestrant	0/1 (0.0)	NE (NE, NE)			
Metastatic setting at last prior CDK4/6 inhibitor therapy (2)					
Alpelisib + Fulvestrant	23/91 (25.3)	NE (18.69, NE)		0.61	(0.36,1.02)
Placebo + Fulvestrant	37/94 (39.4)	22.6 (16.10,28.52)			
Presence of lung/liver metastases (2)					
Alpelisib + Fulvestrant	18/67 (26.9)	NE (15.84, NE)		0.70	(0.38,1.29)
Placebo + Fulvestrant	25/64 (39.1)	23.6 (17.28, NE)			
Absence of lung/liver metastases (2)					
Alpelisib + Fulvestrant	5/27 (18.5)	26.1 (17.64, NE)		0.37	(0.13,1.07)
Placebo + Fulvestrant	12/30 (40.0)	16.1 (10.91, NE)			

(1) Both Log-rank test and Cox PH model are stratified by presence of lung/liver metastases.
(2) Subgroup analysis of stratification factors (per eCRF) uses an unstratified Cox proportional hazards model.
(3) Median (time to event) and its 95% CI are generated by KM estimation.
(4) p-value will only be calculated for 'All participants' group.
(5) Hazard Ratio of Alpelisib + Fulvestrant vs. Placebo + Fulvestrant (Placebo + Fulvestrant is the control).

Figure 4 Kaplan-Meier plot of overall survival (Full Analysis Set)



Stratified Log-rank test and stratified Cox model using strata per IRT defined by (i) Presence of lung and/or liver metastases.
- NE=Not estimable.

Table 17 Reasons for censoring participants in OS analysis (Full Analysis Set)

Study analysis endpoint(s)	Reason of censoring	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)
OS	Number of subjects censored	71 (75.5)	57 (60.6)
	Reason of censoring		
	Alive	64 (68.1)	54 (57.4)
	Lost to follow-up	7 (7.4)	3 (3.2)

Table 18 Overall survival using the RPSFT model – Full Analysis Set

	Alpelisib + Fulvestrant N=94		re-constructed Placebo Fulvestrant N=94
Number of events - n (%)	23 (24.5)		32 (34.0)
Number censored - n (%)	71 (75.5)		62 (66.0)
psi (95% CI)		-0.66 (-1.34, 0.01)	
Hazard ratio (95% CI) Alpelisib + Fulvestrant vs Placebo + Fulvestrant		0.540 (0.288, 1.013)	
Percentiles (95% CI)			
25th	15.67 [11.96, 20.34]		9.49 [5.79, 15.08]
50th (Median)	NE [18.69, NE]		18.86 [15.08, NE]
75th	NE [NE, NE]		NE [NE, NE]
Kaplan-Meier estimates (%) (95% CI)			
1 month	100 [100, 100]		98.9 [92.7, 99.8]
2 months	98.9 [92.5, 99.8]		92.4 [84.7, 96.3]
3 months	97.7 [91.2, 99.4]		91.3 [83.3, 95.5]
6 months	90.4 [81.7, 95.1]		82.4 [72.4, 89.0]
9 months	89.1 [80.0, 94.2]		75.4 [64.4, 83.5]
12 months	84.3 [73.9, 90.9]		65.1 [52.5, 75.0]
15 months	76.7 [64.3, 85.3]		65.1 [52.5, 75.0]
18 months	66.9 [52.4, 77.9]		52.7 [37.6, 65.7]
21 months	61.3 [46.0, 73.5]		48.6 [32.8, 62.7]
24 months	61.3 [46.0, 73.5]		43.2 [26.3, 59.0]
27 months	54.5 [35.6, 70.0]		43.2 [26.3, 59.0]
30 months	NE [NE, NE]		43.2 [26.3, 59.0]
33 months	NE [NE, NE]		NE [NE, NE]

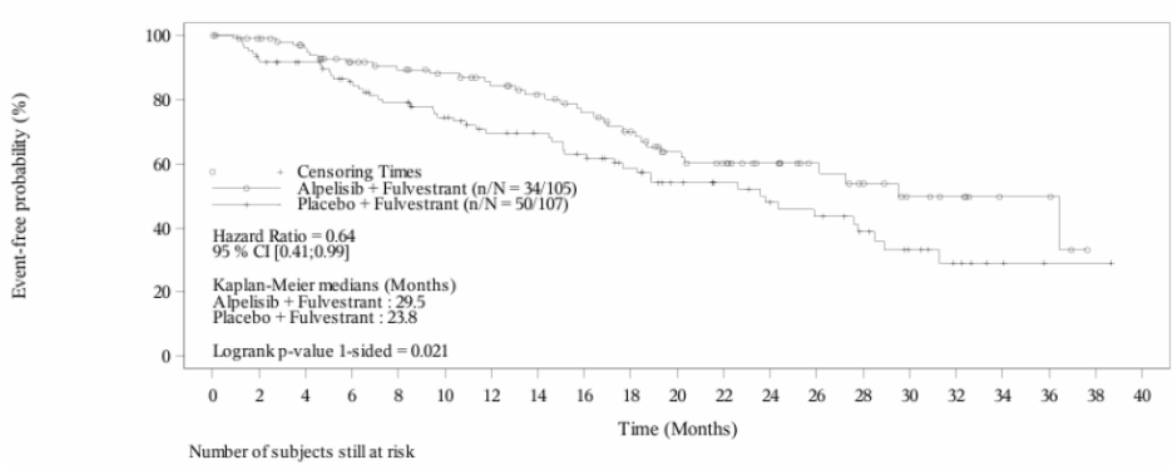
Final OS analysis (DCO: 26-May-2025)

Table 19 Stratified log-rank test and Cox regression model for OS (months), comparison of treatment with control –overall and by eCRF stratification factor - Full Analysis Set

				Cox Model	
	Event/N (%)	Median OS (95% CI) (months) [3]	p-value [4]	Hazard Ratio [5]	95% CI
All participants (1)					
Alpelisib + Fulvestrant	34/105 (32.4)	29.5 (20.17,NE)	0.021	0.64	(0.41,0.99)
Placebo + Fulvestrant	50/107 (46.7)	23.8 (17.28,28.52)			
Adjuvant setting at last prior CDK4/6 inhibitor therapy (2)					
Alpelisib + Fulvestrant	1/1 (100)	16.9 (NE,NE)		NE	(NE,NE)
Placebo + Fulvestrant	0/1 (0.0)	NE (NE,NE)			
Metastatic setting at last prior CDK4/6 inhibitor therapy (2)					
Alpelisib + Fulvestrant	33/102 (32.4)	29.5 (20.17,NE)		0.63	(0.40,0.98)
Placebo + Fulvestrant	50/106 (47.2)	23.6 (17.28,28.52)			
Presence of lung/liver metastases (2)					
Alpelisib + Fulvestrant	27/76 (35.5)	29.5 (18.20,NE)		0.70	(0.42,1.15)
Placebo + Fulvestrant	36/74 (48.6)	23.6 (17.28,27.79)			
Absence of lung/liver metastases (2)					
Alpelisib + Fulvestrant	7/29 (24.1)	NE (20.17,NE)		0.47	(0.19,1.18)
Placebo + Fulvestrant	14/33 (42.4)	23.8 (15.08,NE)			

(1) Both Log-rank test and Cox PH model are stratified by presence of lung/liver metastases.
(2) Subgroup analysis of stratification factors(per eCRF) uses an unstratified Cox proportional hazards mo
(3) Median (time to event) and its 95% CI are generated by KM estimation.
(4) p-value will only be calculated for 'All participants' group.
(5) Hazard Ratio of Alpelisib + Fulvestrant vs. Placebo + Fulvestrant (Placebo + Fulvestrant is the control).

Figure 5 Study C2303 - Kaplan-Meier of overall survival (FAS) with DCO: 26-May-2025



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	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Alpelisib + Fulvestrant	105	103	99	95	91	85	81	77	76	74	71	69	65	63	59	56	53	49	46	41	36	33	31	27	25	22	19	18	15	13	10	9	8	5	4	4	4	1	0	0	0
Placebo + Fulvestrant	107	106	98	94	92	88	81	75	73	68	64	59	56	55	53	51	47	43	39	34	31	30	27	26	23	21	20	19	15	12	10	8	6	4	3	2	1	1	1	0	0

Stratified Log-rank test and stratified Cox model using strata per IRT defined by (i) Presence of lung and/or liver metastases.
- NE=Not estimable.

Table 20 Overall survival using the RPSFT model – FAS (DCO: 26-May-2025)

	Alpelisib + Fulvestrant N=105		re-constructed Placebo + Fulvestrant N=107
Number of events - n (%)	34 (32.4)		47 (44.8)
Number censored - n (%)	71 (67.6)		60 (56.1)
psi (95% CI)		-0.63 (-1.17,-0.03)	
Hazard ratio (95% CI) Alpelisib + Fulvestrant vs Placebo + Fulvestrant		0.515 (0.270, 0.984)	
Percentiles (95% CI)			
25th	16.43 [11.96, 18.69]		7.13 [5.85, 10.91]
50th (Median)	29.50 [20.17, NE]		17.54 [14.27, 22.64]
75th	NE [36.47, NE]		NE [22.64, NE]
Kaplan-Meier estimates (%) (95% CI)			
1 month	100 [100, 100]		99.1 [93.6, 99.9]
2 months	99.0 [93.3, 99.9]		92.5 [85.6, 96.2]
3 months	98.0 [92.3, 99.5]		91.6 [84.4, 95.5]
6 months	91.7 [84.0, 95.7]		82.9 [73.8, 89.0]
9 months	89.3 [81.0, 94.1]		72.4 [62.0, 80.4]
12 months	84.3 [74.8, 90.4]		63.1 [51.9, 72.3]
15 months	78.8 [68.3, 86.1]		58.5 [47.0, 68.4]
18 months	70.0 [58.4, 79.0]		48.1 [36.1, 59.2]
21 months	60.1 [47.7, 70.5]		40.0 [27.3, 52.5]
24 months	60.1 [47.7, 70.5]		36.7 [23.7, 49.8]
27 months	57.0 [43.6, 68.3]		36.7 [23.7, 49.8]
30 months	49.7 [34.6, 63.0]		32.1 [18.6, 46.5]
33 months	49.7 [34.6, 63.0]		32.1 [18.6, 46.5]
36 months	49.7 [34.6, 63.0]		32.1 [18.6, 46.5]
39 months	NE [NE, NE]		NE [NE, NE]

43 placebo plus fulvestrant treated patients (40.2%) with disease progression confirmed by BIRC crossed over to the alpelisib plus fulvestrant arm.

Final PFS and OS analyses (DCO: 26-May-2025)

Table 21 Comparison of efficacy results: primary efficacy analysis vs. final efficacy analysis (study C2303)

Efficacy parameters	C2303 Primary efficacy analysis DCO 15-Oct-2024 Piqray + fulvestrant (n=94)	C2303 Primary efficacy analysis DCO 15-Oct-2024 Placebo + fulvestrant (n=94)	C2303 Final efficacy analysis DCO 26-May-2025 Piqray + fulvestrant (n=105)	C2303 Final efficacy analysis DCO 26-May-2025 Placebo + fulvestrant (n=107)
Primary efficacy endpoint				
Progression-free survival[a]				
Events (progression or death), n (%)	62 (66.0)	79 (84.0)	76 (72.4)	96 (89.7)
Progressions	56 (59.6)	70 (74.5)	67 (63.8)	87 (81.3)
Deaths	6 (6.4)	9 (9.6)	9 (8.6)	9 (8.4)
Median (months) (95% CI)	7.4 (5.52, 9.10)	2.8 (1.94, 3.84)	7.5 (5.78, 9.10)	2.8 (1.97, 3.78)
Hazard ratio (95% CI)[b]	0.52 (0.37, 0.72)		0.48 (0.35, 0.65)	
p-value[c]	<0.0001		<0.0001	
Secondary efficacy endpoint				
Overall survival				
Deaths, n (%)	23 (24.5)	37 (39.4)	34 (32.4)	50 (46.7)
Median, months (95% CI)	NE (18.69, NE)	22.6 (16.10, 28.52)	29.5 (20.17, NE)	23.8 (17.28, 28.52)
Hazard ratio (95% CI)[b]	0.60 (0.36, 1.01)		0.64 (0.41, 0.99)	
Nominal p-value[c]	0.026		0.021	

CI = confidence interval; n = number of patients; NE = not estimable

a Based on BIRC assessment

b Stratified Cox model.

c Both Log-rank test and Cox PH model are stratified by presence of lung/liver metastases. p-value is obtained from a stratified log-rank test at an overall one-sided 2.5% level of significance.

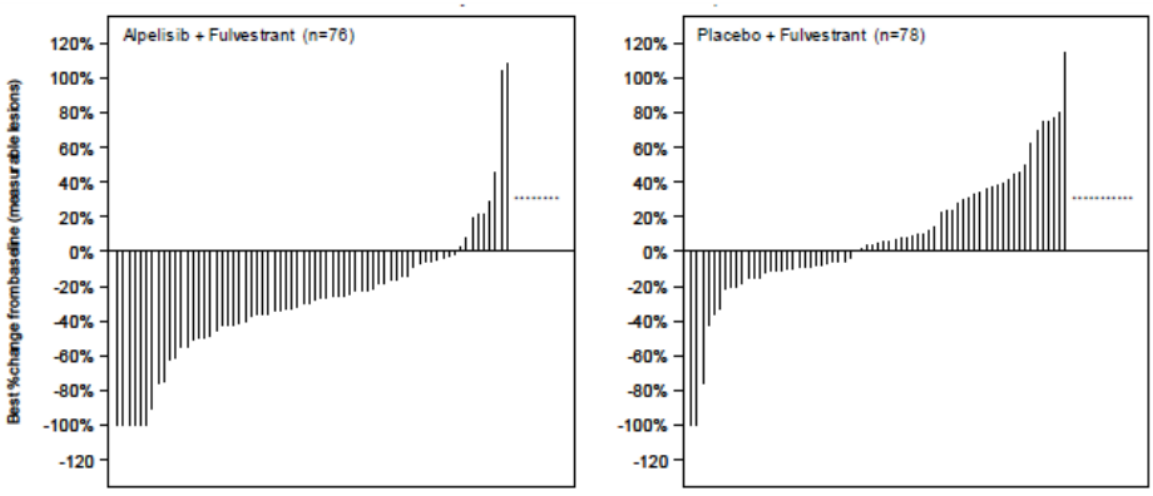
Overall Response Rate with confirmed response

Table 22 Best overall response with confirmed response based on BIRC assessment (Full Analysis Set, Double-blind treatment period)

	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)
Subjects with measurable disease at baseline	85 (90.4)	90 (95.7)
Subjects with non-measurable disease only at baseline	7 (7.4)	3 (3.2)
Best overall response		
Complete response (CR)	2 (2.1)	0
Partial response (PR)	20 (21.3)	4 (4.3)
Stable disease (SD)	30 (31.9)	26 (27.7)
Progressive disease (PD)	24 (25.5)	46 (48.9)
Non-CR/Non-PD (NCRNPD)	5 (5.3)	0
Unknown (UNK)	13 (13.8)	18 (19.1)
Overall response rate (ORR: CR+PR)	22 (23.4)	4 (4.3)
95% CI	(15.3, 33.3)	(1.2, 10.5)
Clinical Benefit Rate (CR+PR+SD+Non-CR/Non-PD ≥24 weeks)	44 (46.8)	20 (21.3)
95% CI	(36.4, 57.4)	(13.5, 30.9)

- N: The total number of subjects in the treatment group. 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 was computed based on the method of Clopper (1934).

Figure 6 Waterfall plot for best percentage change from baseline in sum of diameters based on BIRC assessment (Full Analysis Set, Double-blind treatment period)



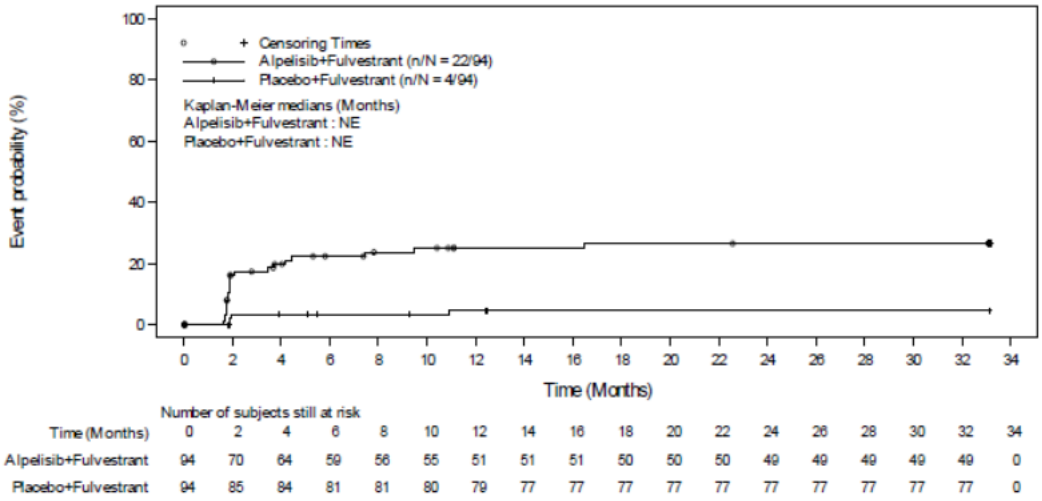
	Alpelisib + Fulvestrant	Placebo + Fulvestrant
Decrease in best percentage change from baseline	77.63%	37.18%
Increase/zero change in best percentage change from baseline	11.84%	48.72%
* % change in target lesion contradicted by Overall lesion response = PD	10.53%	14.10%

Subjects for whom the best % change in target lesions was not available and subjects for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above use n as denominator.
Only subjects with measurable disease at baseline are presented.

Time to response

The median time to confirmed response was not reached for either arm. However, numerical trends were in favor of a shorter time to response in the alpelisib + fulvestrant arm compared with fulvestrant alone. Using Kaplan-Meier methodology for all participants in the FAS, the estimated probability of achieving a response by 6 months was 23.41% (95% CI: 15.58%, 34.29%) in the alpelisib + fulvestrant arm and 3.41% (95% CI: 1.11%, 10.20%) in the placebo + fulvestrant arm.

Figure 7. Kaplan-Meier plot of time to confirmed response as per BIRC assessment (Full Analysis Set, Double-blind treatment period)



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	34
Alpelisib+Fulvestrant	94	70	64	59	56	55	51	51	51	50	50	50	49	49	49	49	49	0
Placebo+Fulvestrant	94	85	84	81	81	80	79	77	77	77	77	77	77	77	77	77	77	0

- Stratified Log-rank test and stratified Cox model using strata per IRT defined by presence of lung and/or liver metastases.

Duration of response

Table 23 Overall summary of duration of response with confirmed response (months) as per BIRC assessment - Full Analysis Set, Double blind treatment period

	Alpelisib + Fulvestrant N=22	Placebo + Fulvestrant N=4
n/N (%)	13/22 (59.1)	1/4 (25.0)
Percentiles (95% CI) [1]:		
25th	5.26 (3.68, 7.39)	7.39 (7.39, NE)
50th	8.64 (4.96,17.68)	NE (7.39, NE)
75th	17.68 (8.64, NE)	NE (7.39, NE)
% Event-free probability estimates (95% CI) [2]:		
3 Months	100.0 (100.0,100.0)	100.0 (100.0,100.0)
6 Months	58.44 (33.60,76.75)	100.0 (100.0,100.0)
9 Months	46.75 (23.47,67.11)	66.67 (5.41,94.52)
12 Months	40.07 (17.95,61.45)	66.67 (5.41,94.52)

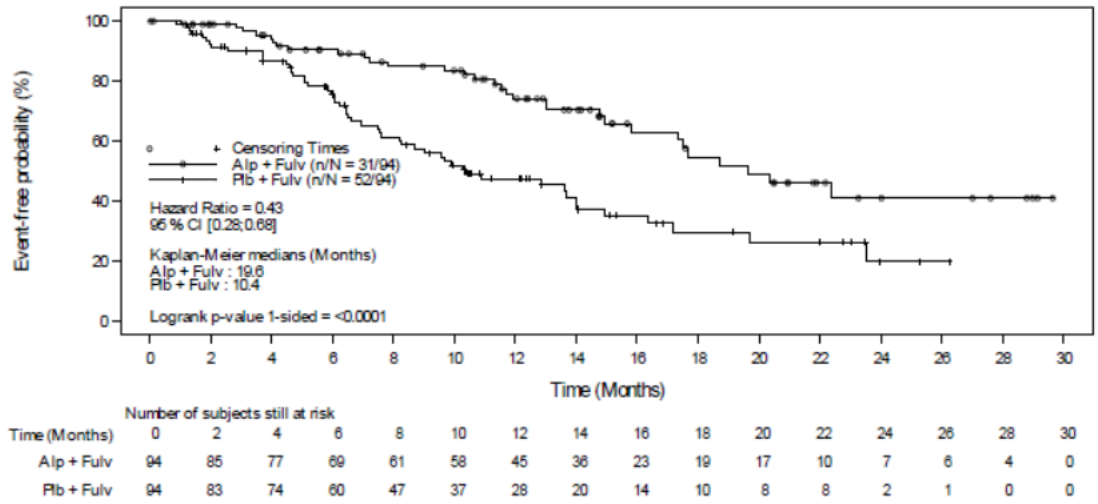
[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
[2] Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point. Event-free probability estimates are obtained from 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.

PFS after next line therapy (PFS2)

Table 24 Summary of type of events for PFS2 as per investigator assessment (FAS)

	Alpelisib + fulvestrant N=94 n (%)	Placebo + fulvestrant N=94 n (%)
Number of PFS events	31 (33.0)	52 (55.3)
PD	16 (17.0)	36 (38.3)
Death	15 (16.0)	16 (17.0)
Number censored	63 (67.0)	42 (44.7)

Figure 8 Kaplan-Meier plot of PFS2 as per investigator assessment (FAS)



Number of subjects still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Alp + Fulv	94	85	77	69	61	58	45	36	23	19	17	10	7	6	4	0
Plb + Fulv	94	83	74	60	47	37	28	20	14	10	8	8	2	1	0	0

Stratified Log-rank test and stratified Cox model using strata per IRT defined by (i) Presence of lung and/or liver metastases.
- NE=Not estimable.

Antineoplastic therapy since discontinuation of study medication

A total of 120 (63.8%) of participants in both arms received antineoplastic therapy since the discontinuation of the study medication (including 22 participants who crossed over to open-label alpelisib + fulvestrant).

Table 25 Antineoplastic therapy since discontinuation of study drug by ATC class and preferred term - Full Analysis Set

		Placebo + Fulvestrant		
	Alpelisib + Fulvestrant N=94 n(%)	Crossover N=34 n(%)	Non crossover N=60 n(%)	All Subjects N=94 n(%)
Any ATC class	60 (63.8)	22 (64.7)	38 (63.3)	60 (63.8)
Anthracyclines and related substances	7 (7.4)	2 (5.9)	7 (11.7)	9 (9.6)
Anti-estrogens	13 (13.8)	2 (5.9)	1 (1.7)	3 (3.2)
Aromatase inhibitors	12 (12.8)	3 (8.8)	6 (10.0)	9 (9.6)
Combinations of antineoplastic agents	0	2 (5.9)	1 (1.7)	3 (3.2)
Cyclin-dependent kinase (CDK) inhibitors	4 (4.3)	0	0	0
Folic acid analogues	0	0	2 (3.3)	2 (2.1)
HER2 (Human epidermal growth factor receptor 2) inhibitors	6 (6.4)	3 (8.8)	6 (10.0)	9 (9.6)
Mammalian target of rapamycin (mTOR) kinase inhibitors	8 (8.5)	4 (11.8)	4 (6.7)	8 (8.5)

Nitrogen mustard analogues	2 (2.1)	2 (5.9)	7 (11.7)	9 (9.6)
Other antineoplastic agents	3 (3.2)	2 (5.9)	3 (5.0)	5 (5.3)
Other cytotoxic antibiotics	0	0	1 (1.7)	1 (1.1)
Other monoclonal antibodies and antibody drug conjugates	0	1 (2.9)	1 (1.7)	2 (2.1)
Phosphatidylinositol-3-kinase (PI3K) inhibitors	0	0	1 (1.7)	1 (1.1)
Platinum compounds	2 (2.1)	0	1 (1.7)	1 (1.1)
Poly (ADP-ribose) polymerase (PARP) Inhibitors	1 (1.1)	0	0	0
Pyrimidine analogues	27 (28.7)	13 (38.2)	16 (26.7)	29 (30.9)
Taxanes	18 (19.1)	9 (26.5)	19 (31.7)	28 (29.8)
VEGF/VEGFR (Vascular endothelial growth factor)	3 (3.2)	0	3 (5.0)	3 (3.2)
Vinca alkaloids and analogues	2 (2.1)	5 (14.7)	6 (10.0)	11 (11.7)

ATC classes are presented alphabetically; preferred terms are sorted within ATC class alphabetically.
A medication / therapy can appear with more than one ATC class.
Open-label alpelisib plus fulvestrant treatment during crossover period is not reported in this analysis.
N in Crossover column includes only those subjects who crossed over to open label alpelisib + fulvestrant treatment.
Crossover column does not include open label alpelisib + fulvestrant treatment

PFS by baseline ctDNA PIK3CA mutation status

Table 26. ***Stratified log-rank test and Cox regression model for PFS (months) based on BIRC assessment, comparison of treatment with control – by PIK3CA mutation status as measured in ctDNA at baseline Full Analysis Set, Double-blind treatment period***

			Cox Model	
	Event/N (%)	Median PFS (95% CI) (months) [3]	Hazard Ratio [4]	95% CI
All participants (1)				
Alpelisib + Fulvestrant	32/44 (72.7)	7.4 (3.98,11.04)	0.39	(0.24,0.64)
Placebo + Fulvestrant	39/45 (86.7)	2.0 (1.84,2.83)		
Adjuvant setting at last prior CDK4/6 inhibitor therapy (2)				
Alpelisib + Fulvestrant	1/1 (100)	1.7 (NE,NE)		
Metastatic setting at last prior CDK4/6 inhibitor therapy (2)				
Alpelisib + Fulvestrant	31/43 (72.1)	7.4 (3.98,11.04)	0.39	(0.24,0.64)
Placebo + Fulvestrant	39/45 (86.7)	2.0 (1.84,2.83)		
Presence of lung/liver metastases (2)				
Alpelisib + Fulvestrant	23/30 (76.7)	7.4 (3.68,11.04)	0.29	(0.16,0.52)
Placebo + Fulvestrant	33/36 (91.7)	1.9 (1.77,1.97)		
Absence of lung/liver metastases (2)				
Alpelisib + Fulvestrant	9/14 (64.3)	9.1 (1.84,NE)	0.90	(0.31,2.62)
Placebo + Fulvestrant	6/9 (66.7)	6.7 (1.87,NE)		

Biomarkers

- PIK3CA mutations in tumor simples

Table 27 Summary of PIK3CA mutation status from tissue biopsy - Full Analysis set, Double blind treatment period

Biomarker Mutational status Mutations	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)
PIK3CA		
n (1)	94	94
Wild Type	0	0
Unknown	1 (1.1)	1 (1.1)
Mutant	94 (100)	94 (100)
C420R	3 (3.2)	3 (3.2)
E542K	22 (23.4)	25 (26.6)
E545A	1 (1.1)	0
E545D	0	2 (2.1)
E545G	0	1 (1.1)
E545K	29 (30.9)	28 (29.8)
H1047L	2 (2.1)	6 (6.4)
H1047R	41 (43.6)	33 (35.1)
H1047Y	1 (1.1)	0
Q546R	0	1 (1.1)

(1) n = number of participants with non-missing somatic mutation status for the considered exons
Participants were enrolled with either the Novartis CTA (based on Cobas assay) or the Qiagen CDx assay. Due to multiplexing strategy, the Cobas assay does not differentiate all mutations and reports E545X for E545A/D/G/K mutations; Q546X for Q546E/R mutations; and H1047X for H1047L/R/Y mutations.
Particiapnts with more than one mutation are counted for each mutation.

- PIK3CA mutation by ctDNA

Table 28 Summary of PIK3CA mutation status from circulating tumor DNA - Full Analysis set, Double blind treatment period

Timepoint: Baseline

Biomarker Mutational status Mutations	Alpelisib + Fulvestrant N=94 n (%)	Placebo + Fulvestrant N=94 n (%)
PIK3CA		
n (1)	60	73
Wild Type	16 (17.0)	28 (29.8)
Mutant	44 (46.8)	45 (47.9)
C420R	1 (1.1)	2 (2.1)
E542K	5 (5.3)	9 (9.6)
E545D	0	1 (1.1)
E545K	11 (11.7)	15 (16.0)
H1047L	2 (2.1)	2 (2.1)
H1047R	25 (26.6)	18 (19.1)

(1) n = number of participants with non-missing somatic mutation status for the considered exons
Participants were enrolled with either the Novartis CTA (based on Cobas assay) or the Qiagen CDx assay. Due to multiplexing strategy, the Cobas assay does not differentiate all mutations and reports E545X for E545A/D/G/K mutations; Q546X for Q546E/R mutations; and H1047X for H1047L/R/Y mutations.
Particiapnts with more than one mutation are counted for each mutation.

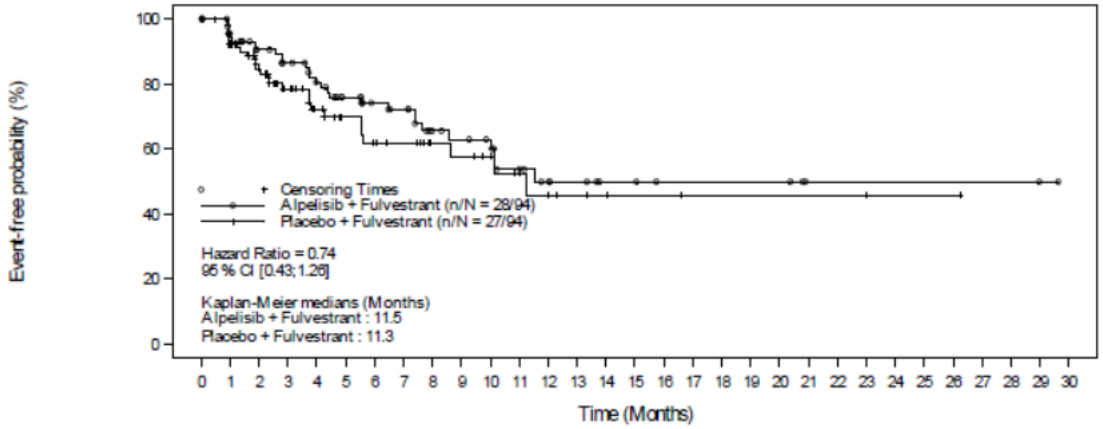
ECOG performance status

Table 29. Overall summary of time to definitive deterioration (months) of ECOG performance status - Full Analysis Set, Double blind treatment period

		Alpelisib + Fulvestrant N=94	Placebo + Fulvestrant N=94
All Participants	n/M (%)	28/94 (29.8)	27/94 (28.7)
	Maximum follow-up	31.57	33.12
	Median follow-up	17.68	17.72
	Median time to censoring	7.16	3.84
	Percentiles (95% CI) [1]:		
	25th	5.55 (3.71, 8.57)	3.71 (1.97, 5.59)
	50th	11.53 (8.57, NE)	11.27 (5.59, NE)
	75th	NE (NE, NE)	NE (NE, NE)
	% Event-free probability estimates (95% CI) [2]:		
	3 Months	86.49 (76.86,92.30)	78.43 (67.34,86.13)
	6 Months	74.19 (62.31,82.82)	61.79 (47.12,73.49)
	9 Months	62.97 (49.04,74.06)	57.67 (41.76,70.69)
	12 Months	49.94 (34.04,63.93)	45.88 (26.75,63.10)

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 participant 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=number of participants with event included in the analysis.
M=number of participants included in the analysis.

Figure 9. Kaplan-Meier plot of time to definitive deterioration (months) of ECOG performance status (Full Analysis Set, Double-blind treatment period)



Stratified Log-rank test and stratified Cox model using strata per IRT defined by (i) Presence of lung and/or liver metastases.

EORTC QLQ-C30

- Double-blind period

Compliance with the EORTC QLQ-C30:

The proportion of participants who completed the EORTC QLQ-30 at baseline was 91.5% and 92.6% in the alpelisib + fulvestrant arm and placebo + fulvestrant arm, respectively. Over time, the compliance to EORTC QLQ-C30 in both arms generally decreased; at Cycle 3 Day 1, the alpelisib + fulvestrant arm had 76.4% compliance while it was 70.6% in the placebo + fulvestrant arm. At the follow-up stages,

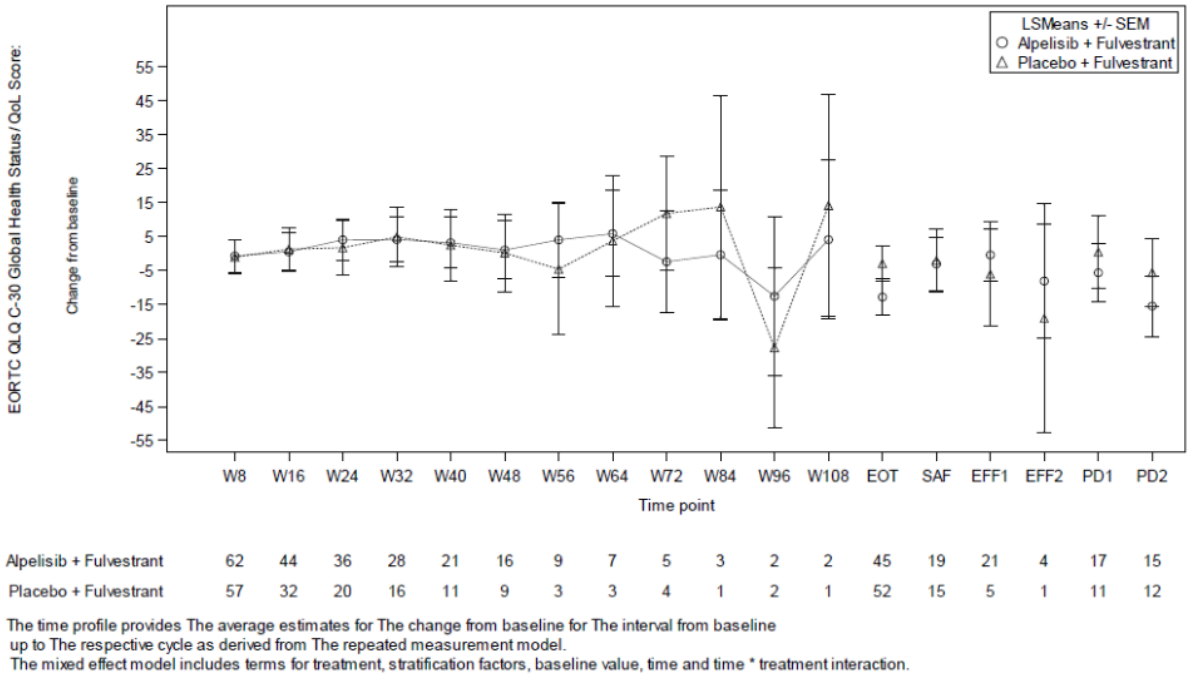
compliance also decreased over time; 50% of participants from the alpelisib + fulvestrant arm had completed the questionnaire during the double-blind EOT stage. The placebo + fulvestrant arm had a similar trend, with 59.6% at double-blind EOT.

EORTC QLQ-C30 Global health status/QOL scale score:

At baseline, both arms had similar numbers of participants and their mean (median) QOL scores were close, with the alpelisib + fulvestrant arm at 66.4 (66.7) and the placebo + fulvestrant arm at 60.6 (66.7). Global health status/QoL scores were generally similar between the two treatment arms throughout the double-blind treatment; there was a slight trend toward a decrease in scores for participants in both the treatment arms.

Analyses of time to 10% deterioration in EORTC global health status/QoL scale, suggested a significantly greater rate of improvement in the alpelisib + fulvestrant arm compared to the placebo + fulvestrant arm at most timepoints (HR=0.56; 95% CI: 0.33, 0.96). The median time to 10% deterioration in EORTC QLQ-C30 global health status/QoL scale score was longer in the alpelisib + fulvestrant arm (9.4 months) compared to the placebo + fulvestrant arm (7.6 months).

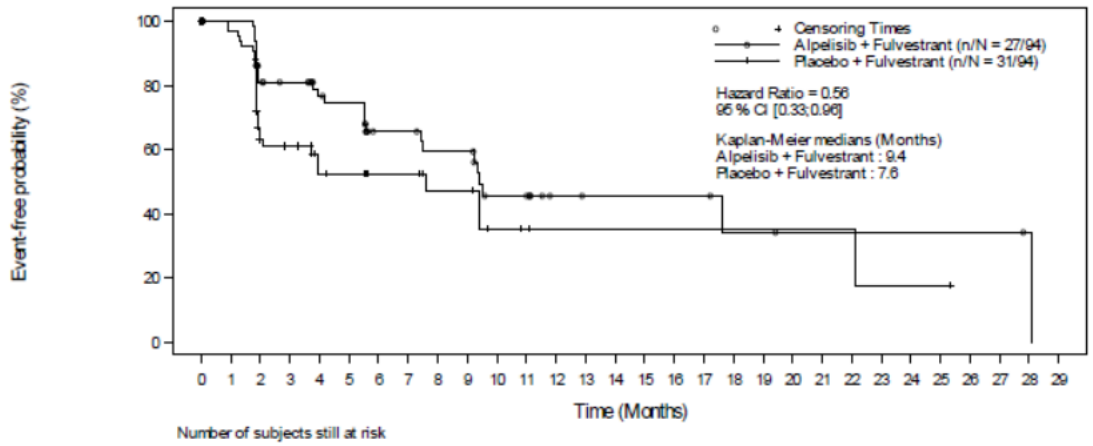
Figure 10 Summary of change from baseline in EORTC QLQ-C30 Global health status/QOL scale score – Full Analysis Set, Double blind treatment period



Alpelisib + Fulvestrant	62	44	36	28	21	16	9	7	5	3	2	2	45	19	21	4	17	15
Placebo + Fulvestrant	57	32	20	16	11	9	3	3	4	1	2	1	52	15	5	1	11	12

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.

Figure 11 Kaplan-Meier plot of time to 10% deterioration in EORTC QLQ-C30 Global health status/QoL scale score (Full Analysis Set, Double-blind treatment period)



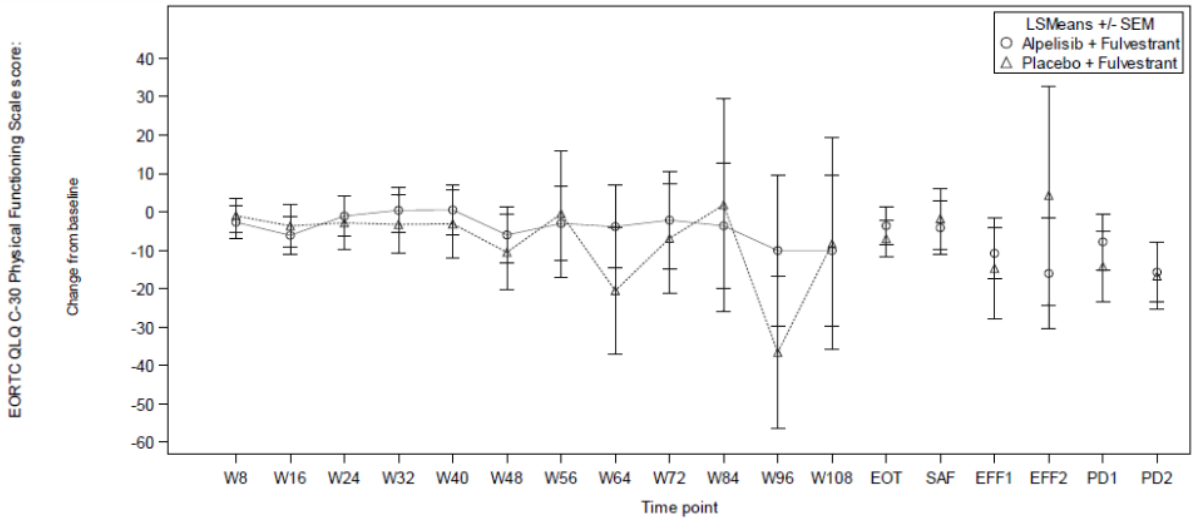
Number of subjects still at risk

Time (Months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Alpelisib + Fulvestrant	94	65	47	44	36	34	22	22	19	19	12	12	6	5	5	5	5	5	3	3	2	2	2	2	2	2	2	1	0	
Placebo + Fulvestrant	94	64	32	30	17	16	13	13	9	9	5	4	2	2	2	2	2	2	2	2	2	2	1	1	1	0	0	0	0	

Stratified Log-rank test and stratified Cox model using strata per IRT defined by (i) Presence of lung and/or liver metastases.

EORTC QLQ-C30 - secondary PRO variables:

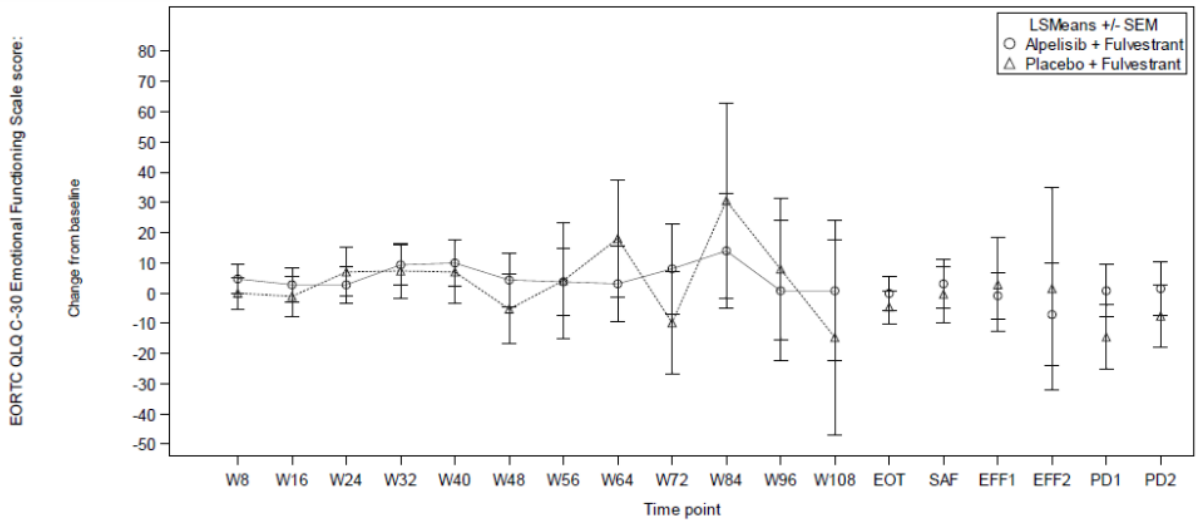
Figure 12 Summary of change from baseline in EORTC QLQ-C30 Physical Functioning Scale score - Full Analysis Set, Double blind treatment period



	W8	W16	W24	W32	W40	W48	W56	W64	W72	W84	W96	W108	EOT	SAF	EFF1	EFF2	PD1	PD2
Alpelisib + Fulvestrant	62	44	36	28	21	16	9	7	5	3	2	2	45	19	21	4	17	15
Placebo + Fulvestrant	57	32	20	16	11	9	3	3	4	1	2	1	52	15	5	1	11	12

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.

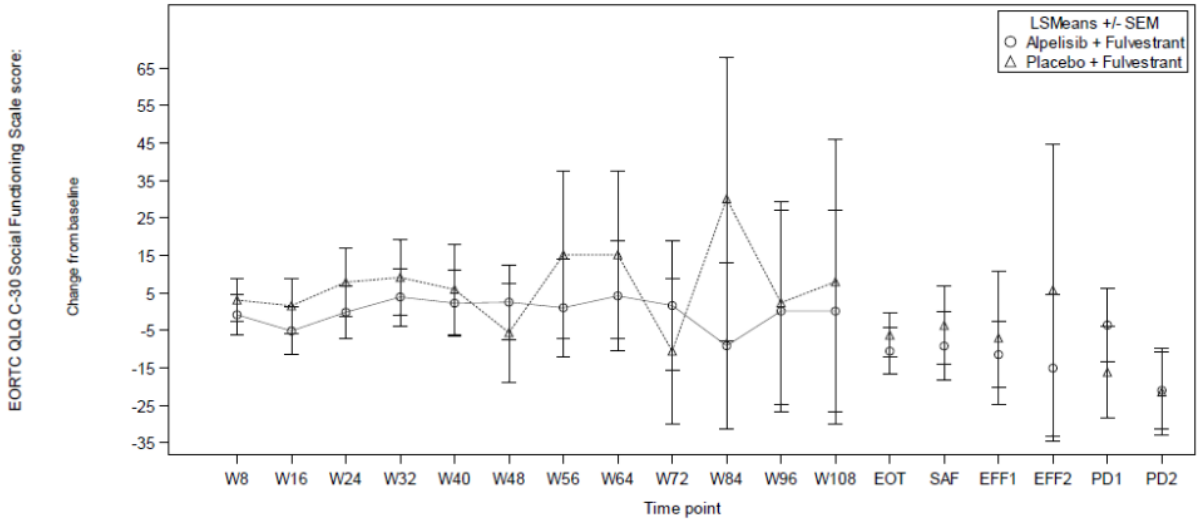
Figure 13 Summary of change from baseline in EORTC QLQ-C30 Emotional Functioning scale score - Full Analysis Set, Double blind treatment period



Alpelisib + Fulvestrant	62	44	36	28	21	16	9	7	5	3	2	2	45	19	21	4	17	15
Placebo + Fulvestrant	57	32	20	16	11	9	3	3	4	1	2	1	52	15	5	1	11	12

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.

Figure 14 Summary of change from baseline in EORTC QLQ-C30 Social Functioning scale score - Full Analysis Set, Double blind treatment period



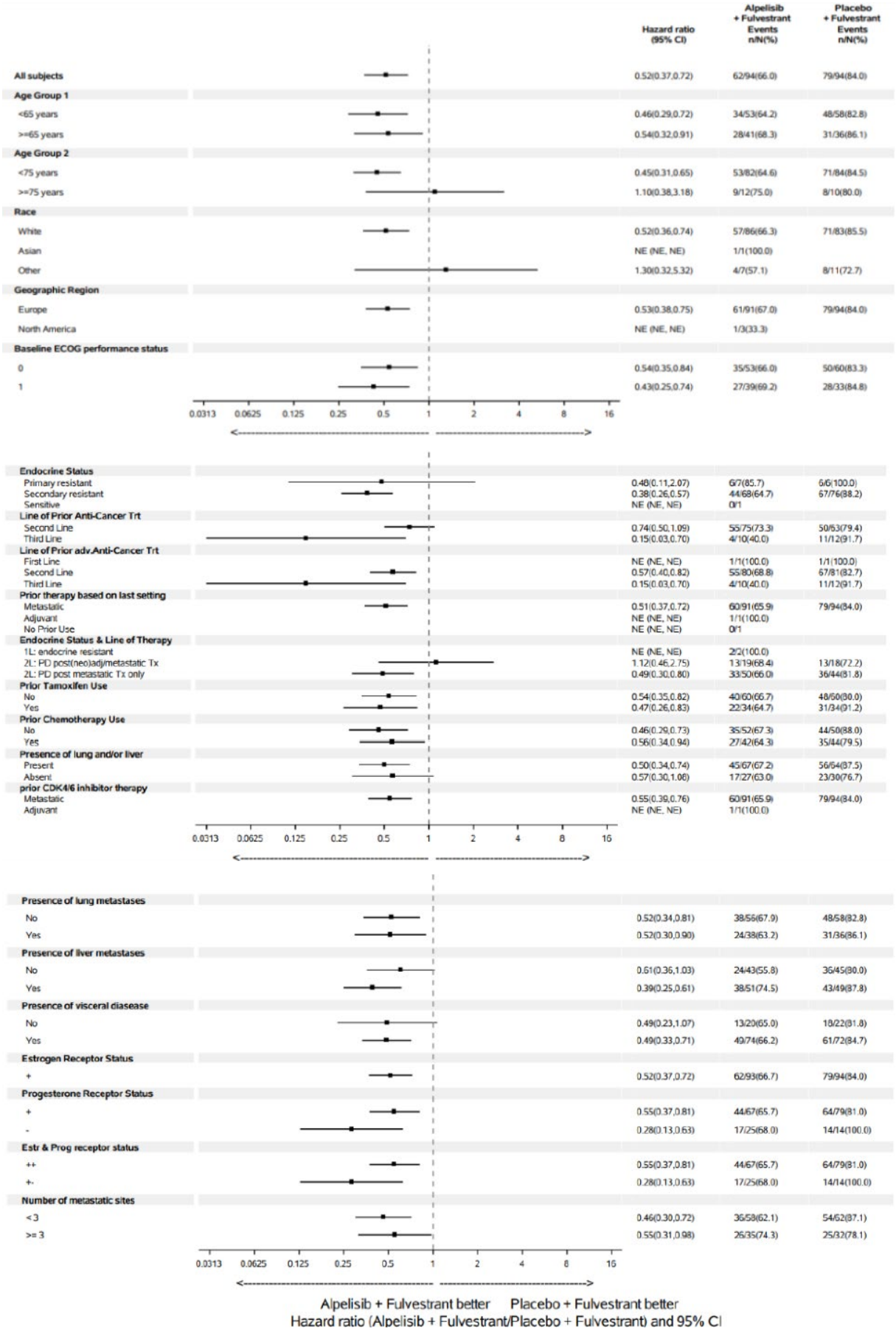
Alpelisib + Fulvestrant	62	44	36	28	21	16	9	7	5	3	2	2	45	19	21	4	17	15
Placebo + Fulvestrant	57	32	20	16	11	9	3	3	4	1	2	1	52	15	5	1	11	12

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.

Ancillary analyses

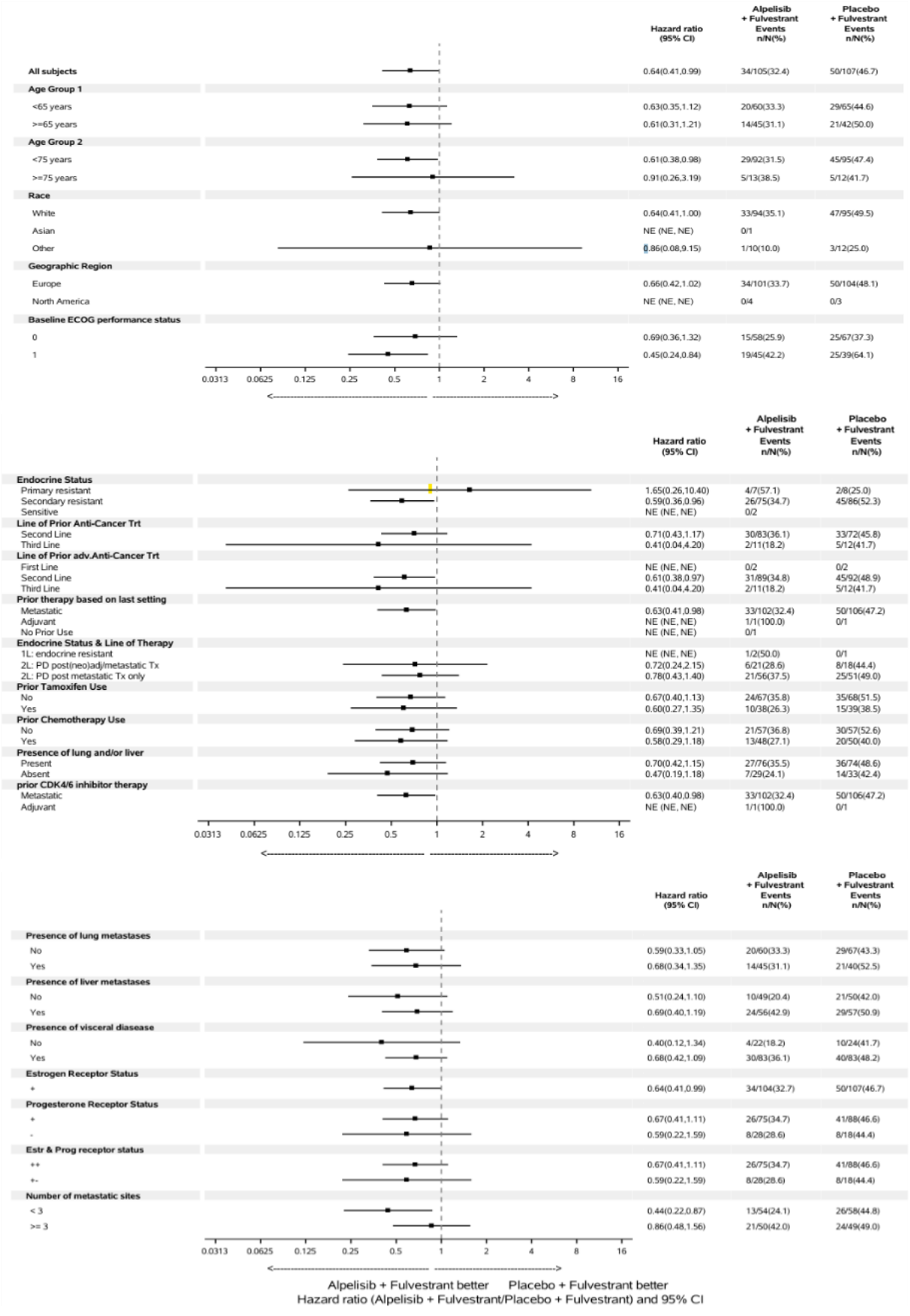
PFS subgroup analyses (DCO: 15-Oct-2024, primary PFS analysis)

Figure 15 Forest plot of hazard ratios for progression-free survival per BIRC assessment – FAS



OS subgroup analyses (DCO: 26-May-2025, final OS analysis)

Figure 16 Forest plot of hazard ratio for overall survival – FAS



Summary of main study(ies)

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

Table 30 Summary of Efficacy for trial C2303

Title: Study C2303 (EPIK-B5): A phase III, randomized, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor		
Study identifier	EUDRACT number: 2021-001966-39 EU CT number: 2023-509133-39-00	
Design	Randomised, double-blind, placebo-controlled, international 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 or relapsed on or after treatment with an AI plus a CDK4/6 inhibitor and with no more than one prior line of chemotherapy in metastatic setting while on or after an endocrine-based treatment	
	Duration of main phase:	Until disease progression, unacceptable toxicity, death, or discontinuation for any other reason.
	Duration of Run-in phase:	Not applicable.
	Duration of Extension phase:	Not applicable.
Hypothesis	Superiority	
Treatments groups	Alpelisib + fulvestrant	Alpelisib 300 mg once daily orally continuously from Cycle 1 Day 1 plus 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). Number randomised at the DCO for the primary PFS analysis: 94 Number randomised at the DCO for the final OS analysis: 105
	Placebo + fulvestrant	Alpelisib matching placebo 300 mg orally once daily continuously from Cycle 1 Day 1 plus 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). Number randomised at the DCO for the primary PFS analysis: 94 Number randomised at the DCO for the final OS analysis: 107

Endpoints and definitions	Primary endpoint	PFS by BIRC	Progression-free survival based on Blinded Independent Review Committee
	Secondary endpoint	OS	Overall survival
Database lock	Primary PFS analysis: 15-Oct-2024 (DCO) Final OS analysis: 26-May-2025 (DCO)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): all subjects who were randomized to study treatment Primary PFS analysis. Final OS analysis		

Descriptive statistics and estimate variability	Treatment group	Alpelisib + fulvestrant	Placebo + fulvestrant
	Number of subjects	94 (primary PFS analysis) 105 (final OS analysis)	94 (primary PFS analysis) 107 (final OS analysis)
	PFS by BICR (events, %)	62/94 (66%)	79/94 (84%)
	Median time (months) (95% CI)	7.4 (5.52, 9.10)	2.8 (1.94, 3.84)
	OS (events, %)	34/105 (32.4%)	50/107 (46.7%)
	Median time (months) (95% CI)	29.8 (20.17, NE)	23.8 (17.28, 28.52)
Effect estimate per comparison	Primary endpoint: PFS by BIRC	Comparison groups	Alpelisib + fulvestrant vs. placebo + fulvestrant
		Hazard Ratio	0.52
		(95% CI)	0.37, 0.72
		P-value	< 0.0001
	Secondary endpoint: OS	Comparison groups	Alpelisib + fulvestrant vs. placebo + fulvestrant
		Hazard Ratio	0.64
		(95% CI)	0.41, 0.99
		P-value	0.021
Notes	PFS analysis had an information fraction of 85% events (141/165) OS was not formally tested.		

Clinical studies in special populations

Table 31 Clinical studies in special populations

	Controlled Phase III Trials***
Renal impairment* patients (Subjects number /total number)	0 / 757
Hepatic impairment** patients (Subjects number /total number)	0 / 757
Paediatric patients <18 years (Subjects number /total number)	0 / 757
Age 65-74 (Subjects number /total number)	232 / 757
Age 75-84 (Subjects number /total number)	90 / 757
Age 85+ (Subjects number /total number)	5 / 757

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C
*** Based on study C2303 (DCO 15-Oct-2024, safety set) and study C2301 (safety set, DCO 15-Oct-2024). No special subject populations were evaluated for renal and hepatic impairment. 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.

In vitro biomarkers test for patient selection for efficacy

Study C2303 prospectively enrolled solely participants with HR+, HER2- advanced breast cancer harbouring a PIK3CA mutation, reflecting the biological and clinical rationale documented in the protocol.

Analytical validation aspects of the assay

Study C2303 allowed confirmation of the PIK3CA mutation status by a Novartis-designated central laboratory using the CE-IVD QIAGEN *therascreen*® PIK3CA RGQ PCR test or by a local laboratory using an FDA-approved PIK3CA companion diagnostic for alpelisib, such as FoundationOne®CDx (F1CDx) or FoundationOne® Liquid CDx (F1LCDx). Laboratory-developed tests (LDTs) or research-use-only versions of the Qiagen assay were explicitly not permitted for enrollment.

Out of 188 randomised patients, 186 patients had their PIK3CA mutation status confirmed by the CE-IVD certified QIAGEN *therascreen*® PIK3CA RGQ PCR test, and 2 patients were enrolled based on PIK3CA test results using FoundationOne®CDx (F1CDx).

- CE-IVD certified QIAGEN therascreen® PIK3CA RGQ PCR Kit

The CE-IVD certified QIAGEN *therascreen*® PIK3CA RGQ PCR Kit is a qualitative PCR test for the detection of 11 mutations in the phosphatidylinositol 3-kinase catalytic subunit alpha (*PIK3CA*) gene (Exon 7: C420R; Exon 9: E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and Exon 20: H1047L, H1047R, H1047Y) using genomic DNA (gDNA) extracted from formalin-fixed, paraffin-embedded (FFPE) breast tumor tissue or circulating tumor DNA (ctDNA) from plasma derived from K2EDTA anticoagulated peripheral whole blood taken from patients with breast cancer.

In Study C2303, the assay was used to screen the PIK3CA mutation status for patient enrollment purposes, following the approved QIAGEN therascreen® PIK3CA RGQ PCR Kit Instructions for Use (IFU, dated September 2019) without deviation.

The test assay used in Study C2303 detects the same 11 hotspot mutations (exons 7, 9, 20) as the assay validated and approved during the initial MAA. Neither the assay reagents nor mutation panel have changed.

The following analytical method characteristics are unchanged from those previously reviewed for the initial MAA:

- Limit of blank (LoB) for tissue and plasma specimens;

- Limit of detection (LoD) for tissue and plasma specimens;
- Genomic DNA input range for tissue and plasma specimens;
- ΔCT cutoff values for tissue and plasma specimens;
- Effect of DNA input on ΔCT values (linearity) for tissue and plasma specimens;
- Assay specificity (cross-reactivity/specificity) for tissue and plasma specimens;
- Interference for tissue and plasma specimens;
- Lot interchangeability for tissue and plasma specimens;
- Repeatability and reproducibility for tissue and plasma specimens;
- Accuracy: Comparison to the analytical reference method for tissue and plasma specimens;
- Cross-contamination/analytical carryover for tissue specimen;
- Blood collection tube validation for plasma specimen.
- FoundationOne®CDx (F1CDx)

With respect to the analytical validation of the FoundationOne®CDx (F1CDx) or FoundationOne® Liquid CDx (F1LCDx) assays, the MAH refers to the corresponding FDA Premarket Approval (PMA) decision summaries and supplements, which provide detailed information on assay performance and validation and as well as the FoundationOne® CDx technical information.

Clinical validation

Although the Study C2303 Protocol does not include an internal tissue vs plasma concordance analysis (as conducted in Study C2301 (SOLAR-1)), the predictive validity of the PIK3CA assay is ensured through the following elements:

- Use of validated regulatory approved companion diagnostics, specifically FDA approved FoundationOne PIK3CA CDx assays and the CE-IVD therascreen® PIK3CA RGQ PCR test, both explicitly permitted in Study C2303 for enrollment and recognized as clinically validated for identifying patients eligible for alpelisib.
- Restriction to a PIK3CAmutant enriched population, consistent with prior evidence demonstrating that therapeutic benefit from PI3Kα inhibition is limited to mutation positive patients.
- Biological and mechanistic rationale, supported by nonclinical data and prior clinical experience, reinforcing that PIK3CA mutations drive PI3K pathway dependence and predict sensitivity to alpelisib, particularly in the post-CDK4/6 inhibitor setting.
- Alignment with regulatory expectations, as both FDA approved CDx assays and CE-IVD certified assays have established analytical and clinical validity to support patient selection for alpelisib.

Therefore, the clinical validity of PIK3CA mutation testing for identifying patients likely to respond to alpelisib is already established, and Study C2303 applies the same validated diagnostic framework—now broadened to include both FDA approved and CE-IVD approved companion diagnostic tests.

Definition of biomarker positivity

PIK3CA-mutation positivity for enrollment in Study C2303 was defined per the FDA-approved or CE-IVD therascreen® test, covering the 11 hotspot mutations (C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y).

A participant was considered PIK3CA-mutation positive if:

- Any hotspot mutation was detected using an approved companion diagnostic, AND
- The result was derived from either tumour tissue or plasma ctDNA using the permitted assays.

The permitted assays use a qualitative cut-off defined by their validated LoD and LoB, which establish the lowest mutant allele level reliably detectable by the assay and the highest signal expected in a true negative sample, respectively.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This submission is supported by Study C2303, a phase III, randomized, double-blind, placebo-controlled study of alpelisib plus fulvestrant in men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer harbouring a PIK3CA mutation after progression on or after an aromatase inhibitor and a CDK4/6 inhibitor. The initial marketing authorisation of Piqray was supported by SOLAR-1 in which very few patients had received a CDK4/6 inhibitor, as these agents were not widely available at the time. Consequently the authorised indication was limited to patients progressing after endocrine therapy as monotherapy.

Of note the SOLAR-1 study has been presented as supportive by the MAH. However, since this study was already assessed for the MA, no further discussion is warranted and reference can be made to the EPAR of the initial MA.

The study randomized patients 1:1 to arm 1 (alpelisib 300 mg + fulvestrant 500 mg) or to arm 2 (placebo + fulvestrant 500 mg). To reflect the use of CDK4/6i in the disease setting, the MAH designed the study C2303 according to the SA recommendations sought in 2021. The comparator and the stratification factors were considered adequate (and were also endorsed in the SA).

The study was double-blind, although considering the characteristic safety profile of alpelisib it can be questioned to what extent blinding was effectively maintained. In any case, the MAH implemented all the possible measures to ensure blindness, such as the assessment of the primary endpoint by BIRC instead of by investigator.

The dose and posology in this study for both alpelisib (300 mg once daily) and fulvestrant (500 mg once daily) were the same as the ones already approved. No changes were proposed regarding the duration of treatment ("*as long as clinical benefit is observed or until unacceptable toxicity occurs*"), which is endorsed since in this study patients were also on treatment until disease progression or unacceptable toxicity.

Inclusion and exclusion criteria were representative of the target population and overall aligned with the inclusion and exclusion criteria established for SOLAR-1. The main differences between both trials were the mandatory prior treatment with a CDK4/6 inhibitor in study C2303 (as in SOLAR-1 it was capped to 30% of the overall population) and the allowance of one line of prior chemotherapy in the metastatic setting in study C2303 (not allowed in SOLAR-1).

The primary (**PFS by BIRC**) and secondary endpoints (**OS, ORR by BIRC**, CBR by BIRC, DoR by BIRC, TTR by BIRC, PFS by BIRC by PIK3CA mutations status in ctDNA at baseline, TDD of ECOG performance status, change from baseline and TTD in QoL and symptom scale scores in EORTC QLQ-C30, and PFS2) are considered acceptable as per the scientific advice (EMA/SA/0000050283). In contrast to the pivotal study SOLAR-1, the primary endpoint PFS in this study is based on BICR assessment, as recommended in the SA, considering the characteristic safety profile of alpelisib+fulvestrant in comparison with fulvestrant alone. The inclusion of PFS2 as a secondary endpoint instead of an exploratory endpoint was also recommended in the SA, with the aim of capturing if there was a detrimental effect compared to the control arm due to a potential drug resistance following endocrine therapy.

Cross-over from the placebo+fulvestrant arm to the alpelisib+fulvestrant arm was permitted for patients who had disease progression as assessed by BIRC. Confirmation of disease progression by BIRC was required. For patients who crossed over, the next disease progression was further determined based on local investigator assessment. The allowance of cross-over was already discussed in the scientific advice and was considered as a limitation although also understandable from a clinical point of view.

There were four **protocol amendments**, which are not considered to have impacted the integrity of the results. The most relevant protocol amendment was amendment 3 (08-Aug-2023), when an efficacy interim analysis (IA) – the only IA of the study- was introduced at approximately 80% of PFS events planned for the final PFS analysis and the number of events needed for this final PFS analysis was slightly increased (from 162 to 165). The MAH added a two-look group-sequential design with the same stopping boundary (O'Brien-Fleming) for both PFS and OS, using an α-spending function to allow for early termination for efficacy. This approach aimed to control the family-wise error rate while evaluating both endpoints at pre-specified interim analyses, which was considered acceptable. Taking into account that the study is double-blind and that this amendment increased the number of events needed for the final PFS analysis while maintaining the same total sample size, it was not concerning.

At the time of the primary PFS analysis, 188 patients completed the screening period and were randomized (94 in each arm). At the DCO there were more patients on treatment in the alpelisib+fulvestrant arm than in the placebo+fulvestrant arm: 20 patients (21.3%) vs. 12 patients (12.8%). The main reason for end of treatment was progressive disease in both arms, being this percentage much higher in the placebo+fulvestrant arm than in the alpelisib+fulvestrant arm (48.9% in alpelisib vs. 76.6% in placebo).

Statistical methods

Sample size

The median PFS in the control arm in participants that progressed on or after AI plus CDK4/6 inhibitor based on literature was assumed to be 5 months and the total sample size was determined to be 234 participants. The assumptions underlying the sample size calculation and the targeted power of 90% were considered acceptable.

It should be noted that while the planned sample size was 234 patients (117 in each arm), at the DCO for the IA (15-Oct-2024) there were only 188 participants enrolled (94 in each arm) and enrolment was still ongoing. The DMC reviewed the results of the IA and recommended to permanently stop the enrolment on 28-Mar-2025, with a total of 212 participants of the planned 234 enrolled. Thus, the IA (i.e., the primary analysis) was based on 188 patients, and the final analysis is based on 212 patients (105 in alpelisib+fulvestrant and 107 in placebo+fulvestrant; DCO: 26-May-2025).

Interim analysis

The interim analysis was based on 141 BIRC assessed PFS events, which represent ~ 85% of the total number of events, with an efficacy boundary of 0.0153. This was considered acceptable, since the MAH stated that the observed number of events at the interim analysis may not be exactly the same as the planned 132 PFS events. Therefore, the efficacy boundary was re-calculated using the prespecified α-spending function.

Estimands

A treatment policy strategy was applied for discontinuation of study treatment, in which data collected after discontinuation of study treatment were used for the primary analysis. This was considered acceptable

Regarding the handling of missing values not related to intercurrent events, "*start of new anti-neoplastic therapy prior to disease progression per BICR or death*" was part of the treatment of interest, which was considered acceptable.

Changes in the planned SAP

The SAP was amended once to align with protocol amendments prior to the database lock for the IA (05-Nov-2024). Upon request, the MAH confirmed that the changes to the SAP were conducted before the analysis database lock (dated 05-Dec-2024), and that the study team and the MAH management were still blinded.

Baseline data

Demographic characteristics

Almost all participants were female (only 2 males were included, both of them in the placebo+fulvestrant arm), which has been adequately reflected in section 5.1 and is understood given the rarity of this disease in men. Median age was 62 years old, and 56.4% of patients were < 65 years old in the alpelisib+fulvestrant arm, vs. 61.7% in the placebo+fulvestrant arm. Therefore, there was a (very) slightly higher rate of patients younger than 65 years old in the alpelisib+fulvestrant arm than in the placebo arm. Almost all patients included in the study were from different EU countries and most patients were White (89.9%). In terms of demographic characteristics, the population included is considered to be representative of the targeted population in the EU.

Disease characteristics

Most patients had an ECOG PS 0 (60.1%), with a slightly higher percentage of ECOG PS 0 in the placebo+fulvestrant arm than in the alpelisib+fulvestrant arm: 63.8% vs. 56.4%.

Almost all patients (98.9%) had stage IV at time of study entry. The majority of patients had bone metastases (82.4%), with 16% of patients in the placebo+fulvestrant arm with only metastases in bone, vs. 6.4% in the alpelisib+fulvestrant arm. Visceral metastases were present in 77.7% of patients, being balanced between arms since it was a stratification factor.

In terms of endocrine resistance, most patients (76.6%) had secondary endocrine resistance, with a small imbalance between arms (72.3% in alpelisib vs. 80.9% in placebo). There were 6.9% of patients with primary endocrine resistance. These percentages are overall similar to the ones reported in SOLAR-1.

In terms of prior therapies, both arms were well-balanced, with most patients having received their last therapy in the metastatic setting (92%). Of note, setting at last prior CDK4/6 inhibitor therapy (adjuvant vs. metastatic) was a stratification factor. However, only 1 patient received a CDK4/6i in the adjuvant setting; meaning that (almost) all patients received it in the metastatic setting. This has been reflected in section 5.1 of the SmPC.

Overall, the demographic and disease baseline characteristics are well-balanced between arms, being reflective of the targeted population. The only slight differences observed (higher percentage in patients with ECOG PS 0 and more patients with only bone metastases) would favour the placebo+fulvestrant arm; therefore, these slight differences are not of concern.

Justification for not pooling the results of study C2303 with the results of C2301 (SOLAR-1)

The efficacy assessment was based on study C2303 rather than pooled efficacy from studies C2303 and C2301 (SOLAR-1), which is endorsed. Pooling was not considered appropriate because of clinically relevant differences between the study populations, and in the assessment of the primary endpoint: PFS *by BIRC* in study C2303 vs. PFS *by investigator* in C2301 (SOLAR-1). The main population difference was prior exposure to a CDK4/6 inhibitor, which was reported in 100% of patients in C2303 compared with 6% in SOLAR-1. Other differences included a lower proportion of non-White patients in C2303 (10.1% versus 33.7%), inclusion of patients who had received chemotherapy in the metastatic setting in C2303 (10.1%), a higher proportion of patients initially diagnosed with stage IV disease in C2303 (43.1% versus 17.6%), a higher proportion of patients with visceral metastases in C2303 (77.7% versus 56.6%), and a lower proportion of patients with only one metastatic site in C2303 (19.7% versus 33.7%). Overall, these differences were considered clinically relevant and precluded pooling the results of the two studies.

Efficacy data and additional analyses

The submitted results are based on the IA (DCO: 15-Oct-2024), with an information fraction of around 85% of the total planned PFS events (141/165) and a median follow-up of 17.7 months. This IA is considered the primary PFS analysis. During the procedure the MAH provided the final PFS and OS results, based on a DCO date of 26-May-2025.

The primary endpoint, **PFS by BIRC**, was statistically significant at the IA, with a HR point estimate of 0.52 (95% CI: 0.37, 0.72; p-value < 0.0001; boundary: 0.0153) and an improvement of 4.6 months in median PFS with alpelisib+fulvestrant compared with placebo+fulvestrant: mPFS was 7.4 months (95% CI: 5.52, 9.10) in alpelisib+fulvestrant and 2.8 months (95% CI: 1.94, 3.84) in placebo+fulvestrant. In the alpelisib+fulvestrant arm there were 62/94 (66%) events, and in the placebo+fulvestrant arm there were 79/94 (84%) events. Most of the reported events in both arms were progressions (56/62, 59.6% in alpelisib vs. 70/79, 74.5% in placebo). There were more censored patients in the alpelisib+fulvestrant arm than in the placebo+fulvestrant arm (32 vs. 15). KM curves separate from the first months, with this separation being maintained over time. PFS by investigator was consistent with the results of the primary analysis [HR: 0.45 (95% CI: 0.32, 0.63)], with an overall concordance rate of 78.7% for the alpelisib+fulvestrant arm and 84% for the placebo+fulvestrant arm. During the assessment the MAH provided the results of the final analysis, which showed consistent results: HR=0.48 (95% CI: 0.35, 0.65); mPFS for alpelisib+fulvestrant: 7.5 months (95% CI: 5.78, 9.10) vs. 2.8 months (95% CI: 1.97, 378) in the placebo+fulvestrant arm. It should be noted that in the final analysis there were additional patients enrolled (105 patients in alpelisib+fulvestrant vs. 107 patients in placebo+fulvestrant) when compared to the IA (94 in each arm).

Of note, mPFS in SOLAR-1 were longer in both the alpelisib+fulvestrant arm (11 months) and the placebo+fulvestrant arm (5.7 months). The reason for such difference is likely related to a poorer prognosis in patients who progressed on endocrine therapy plus a CDK4/6i compared to those who progressed only on endocrine therapy. It is noted that in the study which led to the marketing authorisation of Truqap (capivasertib) in this (almost) same setting (CAPItello-291), (Truqap EPAR), patients in the placebo arm reported a mPFS of 3.1 months (95% CI: 2.0, 3.7) - although these data

should be interpreted with caution because in the CAPItello-291 study not all patients had received a CDK4/6i (70.1% received it), and included patients could have tumours harbouring other gene mutations apart from PIK3CA (i.e., AKT1 and PTEN).

Regarding PFS censoring in the primary analysis, more patients in the alpelisib + fulvestrant arm were ongoing without an event than in the placebo + fulvestrant arm (20.2% vs 12.8%). Censoring for other reasons was also higher with alpelisib + fulvestrant (13.9% vs 3.3%). Discontinuations due to clinical progression without RECIST 1.1 confirmation were not counted as PFS events; however, a sensitivity analysis including these 6 cases as progression events gave results consistent with the main analysis.

There was an imbalance in the stratification factor "*adjuvant setting at last prior CDK4/6 inhibitor*", as almost all patients had received a CDK4/6 inhibitor in the metastatic setting. It was clarified in the SAP dated 05-Nov-2024, after the 15-Oct-2024 DCO, that stratification would rely only on lung and/or liver metastases per IRT. This was considered acceptable, as pre-planned unstratified and supplementary multivariate Cox analyses were consistent with the primary analysis (HRs 0.51–0.55 vs 0.52). Additional supplementary analyses, including alternative censoring and stratification approaches, also supported the robustness of the primary PFS result.

A descriptive **OS** improvement was observed, with consistent results at IA (HR 0.60; 95% CI: 0.36, 1.01; nominal p=0.026) and FA (HR 0.64; 95% CI: 0.41, 0.99; nominal p=0.021). At FA, deaths occurred in 34/105 patients in the alpelisib + fulvestrant arm versus 50/107 in the placebo + fulvestrant arm, with median OS of 29.5 versus 23.8 months, respectively. Kaplan-Meier curves separated from month 4 and remained separated. Cross-over occurred in 43 patients from the placebo-arm; an RPSFT analysis adjusting for cross-over supported the OS trend (HR 0.52; 95% CI: 0.27, 0.98). OS subgroup analyses were generally consistent with the overall population, with minor differences likely reflecting small subgroup sizes.

ORR and **CBR by BIRC**, although not multiplicity-protected, favoured alpelisib + fulvestrant over placebo + fulvestrant (23.4% vs 4.3% and 46.8% vs 21.3%, respectively), with tumour shrinkage in 77.6% versus 37.2% of patients. PFS2 also supported the primary result (HR 0.43; 95% CI: 0.28, 0.68; median 19.6 vs 10.4 months), with no apparent detrimental longer-term effect. PRO data showed broadly similar QoL between arms, but interpretation is limited by declining compliance and potential unblinding.

2.4.4. Conclusions on the clinical efficacy

Alpelisib in combination with fulvestrant has demonstrated a clinically relevant and statistically significant improvement in delaying the tumour progression in patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy in combination with a CDK4/6 inhibitor. An improvement in OS, was also observed, although the analysis was descriptive.

2.5. Clinical safety

Introduction

The safety evaluation for this variation procedure is based on the pooled analysis of the studies C2303 and C2301 (SOLAR-1). Overall, when considering the clinical safety aspects, both clinical trials share a similar design and comparable populations. The main difference is that study C2303 included exclusively patients previously treated with CDK4/6 and aromatase inhibitors, while only 20 (out of 571) patients had received prior CDK4/6 inhibitors within the SOLAR-1 study.

In the C2303 experimental arm, two participants did not receive any study medication and were therefore excluded from the safety population. The safety results refer to all participants treated during the double-blind phase.

In total, 376 participants have been exposed to alpelisib plus fulvestrant across the two studies.

Table 32. Overview of clinical studies that contributed to safety data.

Key features	C2303	C2301 (SOLAR-1)
Controlled study	Yes	Yes
Phase	III	III
Study design	Double-blind, randomized, placebo controlled	Double-blind, randomized, placebo controlled
Population	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease progressed on or after aromatase inhibitor-based treatment
Dose	300 mg alpelisib q.d. administered orally, together with fulvestrant 500 mg intramuscularly (i.m.) on Days 1 and 15 of Cycle (month) 1, thereafter on Day◦1 of every cycle (month)	300 mg alpelisib q.d. administered orally together with fulvestrant 500 mg intramuscularly (i.m.) on Days 1 and 15 of Cycle (month) 1, thereafter on Day◦1 of every cycle (month)
Treatment duration	Until disease progression per RECIST v1.1 as per BIRC assessment, unacceptable toxicity that precludes further treatment, or until discontinuation of study treatment due to any other reason	Until disease progression (radiologically documented according to RECIST 1.1) or until discontinuation of study treatment due to any other reason.
No. participants (total)	188 (188 with PIK3CA mutation)	571 (340 with PIK3CA mutation)
No. randomized/treated	Alpelisib + Fulvestrant: 94/92	Alpelisib + Fulvestrant: 284/284
	Placebo + Fulvestrant: 94/94	Placebo + Fulvestrant: 287/287
Completed/Ongoing	Ongoing	Completed
	Data cut-off: 15-Oct-2024	LPLV: 9-Jun-2023

Table 33. Participants in the pooled safety set

Pooled treatment group	Study	No. of participants in study safety set	No. of participants in safety pool
Alpelisib + Fulvestrant	C2303	92*	376
	C2301 (SOLAR-1)	284	

Placebo + Fulvestrant	C2303	94	381
	C2301 (SOLAR-1)	287	

*94 participants were randomized to the alpelisib + fulvestrant arm, but 2 participants never received any study treatment and were excluded from the safety set.

Patient exposure

As of the data cut-off (15-Oct-2024), in study C2303, the median duration of exposure to alpelisib + fulvestrant was 5.6 months (range: 0.5-29.9) and 3.0 months (range: 0.5-26.8) in the placebo + fulvestrant arm. A total of 47.8% of participants in the alpelisib arm and 26.6% in the placebo arm were treated for at least 6 months. At 18 months, exposure was reported for 5.4% of participants in the alpelisib arm and 2.1% in the placebo arm.

In the pooled safety set, the median duration of exposure to alpelisib plus fulvestrant was 7.4 months (range: 0.4–77.4), and 4.6 months (range: 0.5–58.9) in the placebo plus fulvestrant arm. Exposure rates at different timepoints are presented in Table 34.

Table 34 Duration of exposure to study treatment

	C2303		**C2301**		**Pool**	
Duration	**Alpelisib + Fulv N = 92 n (%)**	**Placebo + Fulv N = 94 n (%)**	**Alpelisib + Fulv N = 284 n (%)**	**Placebo + Fulv N = 287 n (%)**	**Alpelisib + Fulv N = 376 n (%)**	**Placebo+ Fulv N = 381 n (%)**
Less than 1 month	4 (4.3)	7 (7.4)	15 (5.3)	9 (3.1)	19 (5.1)	16 (4.2)
at least 1 month	88 (95.7)	87 (92.6)	269 (94.7)	278 (96.9)	357 (94.9)	365 (95.8)
at least 2 months	73 (79.3)	65 (69.1)	246 (86.6)	223 (77.7)	319 (84.8)	288 (75.6)
at least 3 months	67 (72.8)	46 (48.9)	231 (81.3)	192 (66.9)	298 (79.3)	238 (62.5)
at least 4 months	60 (65.2)	39 (41.5)	205 (72.2)	161 (56.1)	265 (70.5)	200 (52.5)
at least 6 months	44 (47.8)	25 (26.6)	168 (59.2)	141 (49.1)	212 (56.4)	166 (43.6)
at least 12 months	18 (19.6)	7 (7.4)	102 (35.9)	85 (29.6)	120 (31.9)	92 (24.1)
at least 18 months	5 (5.4)	2 (2.1)	70 (24.6)	62 (21.6)	75 (19.9)	64 (16.8)
Participant-time (months)					4577.6	3607.2

Pooled participants refer to participants in Study C2303, excluding data during the crossover period from participants who switched from placebo + fulvestrant to open-label alpelisib + fulvestrant and in Study C2301 (SOLAR-1) regardless of mutation status.
Participant-time is the sum of each participant's treatment exposure in months.

At the data cut-off for Study C2303, 72 participants (78.3%) in the alpelisib plus fulvestrant arm and 82 participants (87.2%) in the placebo plus fulvestrant arm had discontinued treatment. The most common reason for treatment discontinuation in both groups was disease progression, occurring in 50.0% of participants in the alpelisib arm and 76.6% in the placebo arm.

Discontinuation due to adverse events (AEs) was more frequent in the alpelisib arm than in the placebo arm (15.2% vs 4.3%, respectively). Among participants treated with alpelisib, the rate of treatment discontinuation due to AEs was higher in Study C2303 compared with Study C2301.

Table 35 Participant disposition in safety set

	C2303		C2301		Pool	
Disposition Reason	**Alpelisib + Fulv N = 92 n (%)**	**Placebo + Fulv N = 94 n (%)**	**Alpelisib + Fulv N = 284 n (%)**	**Placebo + Fulv N = 287 n (%)**	**Alpelisib + Fulv N = 376 n (%)**	**Placebo+ Fulv N = 381 n (%)**
Participants treated						
Treatment ongoing*	20 (21.7)	12 (12.8)	0	0	20 (5.3)	12 (3.1)
End of treatment	72 (78.3)	82 (87.2)	284 (100)	287 (100)	356 (94.7)	369 (96.9)
Primary reason for end of treatment						
Progressive Disease	46 (50.0)	72 (76.6)	207 (72.9)	240 (83.6)	253 (67.3)	312 (81.9)
Physician Decision	7 (7.6)	3 (3.2)	29 (10.2)	22 (7.7)	36 (9.6)	25 (6.6)
Adverse Event	14 (15.2)	4 (4.3)	14 (4.9)	4 (1.4)	28 (7.4)	8 (2.1)
Participant/Guardian Decision	0	0	24 (8.5)	11 (3.8)	24 (6.4)	11 (2.9)
Death	4 (4.3)	2 (2.1)	4 (1.4)	4 (1.4)	8 (2.1)	6 (1.6)
Protocol Deviation	0	0	5 (1.8)	6 (2.1)	5 (1.3)	6 (1.6)
Participant Decision	1 (1.1)	1 (1.1)	0	0	1 (0.3)	1 (0.3)
Study Terminated By Sponsor	0	0	1 (0.4)	0	1 (0.3)	0

* Participants ongoing at the time of the cut-off 15-Oct-2024
^ Participants 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
Percentage is based on N
Reason for not being treated is from CRF completion page

Adverse events

During the double-blind period of Study C2303, 100% of the participants allocated to the alpelisib and fulvestrant arm presented an AE, compared with 86.2% in the placebo and fulvestrant. Treatment-related AEs were reported in 97.8% of participants receiving alpelisib and in 58.5% of those in the placebo arm.

The incidence of severe adverse events (SAEs) was similar between treatment groups in study C2303 (22.8% in the alpelisib arm vs 20.7% in the placebo arm). However, the proportion of patients with SAEs and treatment related SAEs were lower in C2303 study compared with C2301 (SOLAR-1) study.

The number of patients with a fatal SAE in Study C2303 was comparable between groups (4.3% in alpelisib group and 3.2% in control group). The frequency of AEs leading to dose discontinuation or dose interruption/modification was generally similar across treatment arms and between the two studies. A comprehensive overview of the AE results is provided in Table 36 .

Table 36 Overview of adverse events (Safety Set)

	C2303				C2301				Pool			
	Alpelisib +Fluv N=92		Placebo +Fluv N=94		Alpelisib + Fluv N=284		Placebo + Fluv N=287		Alpelisib + Fluv N=376		Placebo + Fluv N=381	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Adverse events	92 (100)	65 (70.7)	81 (86.2)	31 (33.0)	282 (99.3)	224 (78.9)	267 (93.0)	107 (37.3)	374 (99.5)	289 (76.9)	348 (91.3)	138 (36.2)
Treatment-related	90 (97.8)	60 (65.2)	55 (58.5)	12 (12.8)	265 (93.3)	192 (67.6)	184 (64.1)	34 (11.8)	355 (94.4)	252 (67.0)	239 (62.7)	46 (12.1)
SAEs	21 (22.8)	19 (20.7)	18 (19.1)	14 (14.9)	110 (38.7)	93 (32.7)	54 (18.8)	48 (16.7)	131 (34.8)	112 (29.8)	72 (18.9)	62 (16.3)
Treatment-related	12 (13.0)	11 (12.0)	2 (2.1)	1 (1.1)	67 (23.6)	55 (19.4)	5 (1.7)	4 (1.4)	79 (21.0)	66 (17.6)	7 (1.8)	5 (1.3)
Fatal SAEs	4 (4.3)	4 (4.3)	3 (3.2)	3 (3.2)	4 (1.4)	4 (1.4)	4 (1.4)	4 (1.4)	8 (2.1)	8 (2.1)	7 (1.8)	7 (1.8)
Treatment-related	1 (1.1)	1 (1.1)	0	0	1 (0.4)	1 (0.4)	0	0	2 (0.5)	2 (0.5)	0	0
AEs leading to discontinuation	26 (28.3)	16 (17.4)	7 (7.4)	4 (4.3)	75 (26.4)	37 (13.0)	16 (5.6)	11 (3.8)	101 (26.9)	53 (14.1)	23 (6.0)	15 (3.9)
Treatment-related	24 (26.1)	15 (16.3)	0	0	65 (22.9)	29 (10.2)	11 (3.8)	8 (2.8)	89 (23.7)	44 (11.7)	11 (2.9)	8 (2.1)
AEs leading to dose adjustment/interruption	73 (79.3)	57 (62.0)	20 (21.3)	15 (16.0)	228 (80.3)	185 (65.1)	67 (23.3)	43 (15.0)	301 (80.1)	242 (64.4)	87 (22.8)	58 (15.2)
AEs requiring additional therapy	90 (97.8)	57 (62.0)	58 (61.7)	17 (18.1)	278 (97.9)	195 (68.7)	203 (70.7)	76 (26.5)	368 (97.9)	252 (67.0)	261 (68.5)	93 (24.4)

Numbers (n) represent counts of participants.
A participant with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 27.1, CTCAE version 4.03.

Common adverse events

In the pooled safety set, the AE profile was consistent with findings from Study C2303 (Table 37). Among all-grade AEs, three additional events reached a frequency ≥15% in the alpelisib plus fulvestrant group: alopecia (16.8% vs 1.8%), pyrexia (16.2% vs 6.0%), and headache (15.4% vs 11.3). Grade ≥3 AEs with a frequency ≥5% were the same as those observed in Study C2303, with the exception of diarrhoea, which reached 6.1% in the pooled alpelisib group vs 0.5% in the placebo group.

Table 37 Adverse events by preferred term (>10% participants in any group) and maximum grade (Safety Set)

	C2303				C2301 (SOLAR-1)				Pool			
	Alpelisib + Fluv N=92		Placebo + Fluv N=94		Alpelisib + Fluv N=284		Placebo + Fluv N=287		Alpelisib + Fluv N=376		Placebo + Fluv N=381	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Number of participants with at least one event	92 (100)	65 (70.7)	81 (86.2)	31 (33.0)	282 (99.3)	224 (78.9)	267 (93.0)	107 (37.3)	374 (99.5)	289 (76.9)	348 (91.3)	138 (36.2)
Hyperglycaemia	67 (72.8)	30 (32.6)	11 (11.7)	0	185 (65.1)	106 (37.3)	27 (9.4)	3 (1.0)	252 (67.0)	136 (36.2)	38 (10.0)	3 (0.8)
Diarrhoea	47 (51.1)	2 (2.2)	11 (11.7)	0	170 (59.9)	21 (7.4)	48 (16.7)	2 (0.7)	217 (57.7)	23 (6.1)	59 (15.5)	2 (0.5)
Nausea	41 (44.6)	1 (1.1)	13 (13.8)	0	133 (46.8)	8 (2.8)	65 (22.6)	1 (0.3)	174 (46.3)	9 (2.4)	78 (20.5)	1 (0.3)
Decreased appetite	28 (30.4)	4 (4.3)	6 (6.4)	0	105 (37.0)	3 (1.1)	30 (10.5)	1 (0.3)	133 (35.4)	7 (1.9)	36 (9.4)	1 (0.3)
Rash	28 (30.4)	12 (13.0)	1 (1.1)	0	103 (36.3)	28 (9.9)	20 (7.0)	1 (0.3)	131 (34.8)	40 (10.6)	21 (5.5)	1 (0.3)
Vomiting	17 (18.5)	0	6 (6.4)	0	84 (29.6)	2 (0.7)	29 (10.1)	1 (0.3)	101 (26.9)	2 (0.5)	35 (9.2)	1 (0.3)
Weight decreased	14 (15.2)	5 (5.4)	1 (1.1)	0	80 (28.2)	17 (6.0)	7 (2.4)	0	94 (25.0)	22 (5.9)	8 (2.1)	0
Asthenia	25 (27.2)	4 (4.3)	15 (16.0)	0	64 (22.5)	7 (2.5)	40 (13.9)	0	89 (23.7)	11 (2.9)	55 (14.4)	0
Stomatitis	15 (16.3)	4 (4.3)	2 (2.1)	1 (1.1)	72 (25.4)	7 (2.5)	20 (7.0)	0	87 (23.1)	11 (2.9)	22 (5.8)	1 (0.3)
Fatigue	13 (14.1)	0	8 (8.5)	1 (1.1)	73 (25.7)	10 (3.5)	51 (17.8)	3 (1.0)	86 (22.9)	10 (2.7)	59 (15.5)	4 (1.0)
Mucosal inflammation	20 (21.7)	3 (3.3)	0	0	53 (18.7)	6 (2.1)	4 (1.4)	0	73 (19.4)	9 (2.4)	4 (1.0)	0
Alopecia	5 (5.4)	0	0	0	58 (20.4)	0	7 (2.4)	0	63 (16.8)	0	7 (1.8)	0
Pruritus	7 (7.6)	1 (1.1)	2 (2.1)	0	54 (19.0)	2 (0.7)	19 (6.6)	0	61 (16.2)	3 (0.8)	21 (5.5)	0
Pyrexia	13 (14.1)	1 (1.1)	7 (7.4)	0	48 (16.9)	2 (0.7)	16 (5.6)	1 (0.3)	61 (16.2)	3 (0.8)	23 (6.0)	1 (0.3)
Headache	4 (4.3)	0	5 (5.3)	0	54 (19.0)	2 (0.7)	38 (13.2)	0	58 (15.4)	2 (0.5)	43 (11.3)	0
Oedema peripheral	7 (7.6)	0	1 (1.1)	0	46 (16.2)	0	14 (4.9)	0	53 (14.1)	0	15 (3.9)	0
Arthralgia	8 (8.7)	1 (1.1)	15 (16.0)	0	44 (15.5)	1 (0.4)	57 (19.9)	4 (1.4)	52 (13.8)	2 (0.5)	72 (18.9)	4 (1.0)
Rash maculo-papular	10 (10.9)	7 (7.6)	0	0	41 (14.4)	25 (8.8)	4 (1.4)	0	51 (13.6)	32 (8.5)	4 (1.0)	0
Back pain	3 (3.3)	0	7 (7.4)	1 (1.1)	44 (15.5)	5 (1.8)	43 (15.0)	5 (1.7)	47 (12.5)	5 (1.3)	50 (13.1)	6 (1.6)

Blood creatinine increased	11 (12.0)	0	1 (1.1)	0	36 (12.7)	5 (1.8)	4 (1.4)	0	47 (12.5)	5 (1.3)	5 (1.3)	0
Dry skin	3 (3.3)	0	2 (2.1)	0	44 (15.5)	0	10 (3.5)	0	47 (12.5)	0	12 (3.1)	0
Dysgeusia	8 (8.7)	0	1 (1.1)	0	39 (13.7)	0	8 (2.8)	0	47 (12.5)	0	9 (2.4)	0
Anaemia	12 (13.0)	0	12 (12.8)	1 (1.1)	34 (12.0)	14 (4.9)	20 (7.0)	4 (1.4)	46 (12.2)	14 (3.7)	32 (8.4)	5 (1.3)
Aspartate aminotransferase in creased	9 (9.8)	3 (3.3)	13 (13.8)	6 (6.4)	32 (11.3)	9 (3.2)	18 (6.3)	6 (2.1)	41 (10.9)	12 (3.2)	31 (8.1)	12 (3.1)
Abdominal pain	4 (4.3)	1 (1.1)	3 (3.2)	1 (1.1)	36 (12.7)	4 (1.4)	21 (7.3)	4 (1.4)	40 (10.6)	5 (1.3)	24 (6.3)	5 (1.3)
Dyspepsia	6 (6.5)	1 (1.1)	2 (2.1)	0	33 (11.6)	0	17 (5.9)	0	39 (10.4)	1 (0.3)	19 (5.0)	0
Cough	2 (2.2)	0	4 (4.3)	1 (1.1)	36 (12.7)	1 (0.4)	28 (9.8)	0	38 (10.1)	1 (0.3)	32 (8.4)	1 (0.3)
Dry mouth	8 (8.7)	0	0	0	30 (10.6)	1 (0.4)	13 (4.5)	0	38 (10.1)	1 (0.3)	13 (3.4)	0
Alanine aminotransferase in creased	7 (7.6)	3 (3.3)	14 (14.9)	5 (5.3)	28 (9.9)	10 (3.5)	18 (6.3)	7 (2.4)	35 (9.3)	13 (3.5)	32 (8.4)	12 (3.1)
Urinary tract infection	6 (6.5)	0	4 (4.3)	0	29 (10.2)	2 (0.7)	16 (5.6)	3 (1.0)	35 (9.3)	2 (0.5)	20 (5.2)	3 (0.8)
Pain in extremity	5 (5.4)	0	2 (2.1)	1 (1.1)	29 (10.2)	0	24 (8.4)	1 (0.3)	34 (9.0)	0	26 (6.8)	2 (0.5)
Dyspnoea	4 (4.3)	1 (1.1)	6 (6.4)	0	29 (10.2)	3 (1.1)	34 (11.8)	6 (2.1)	33 (8.8)	4 (1.1)	40 (10.5)	6 (1.6)
Hypertension	4 (4.3)	0	2 (2.1)	0	29 (10.2)	15 (5.3)	15 (5.2)	9 (3.1)	33 (8.8)	15 (4.0)	17 (4.5)	9 (2.4)
Hypokalaemia	4 (4.3)	2 (2.2)	1 (1.1)	1 (1.1)	28 (9.9)	13 (4.6)	5 (1.7)	1 (0.3)	32 (8.5)	15 (4.0)	6 (1.6)	2 (0.5)
Gamma-glutamyltransferase increased	3 (3.3)	1 (1.1)	14 (14.9)	7 (7.4)	28 (9.9)	12 (4.2)	23 (8.0)	17 (5.9)	31 (8.2)	13 (3.5)	37 (9.7)	24 (6.3)
Dizziness	2 (2.2)	0	1 (1.1)	0	27 (9.5)	1 (0.4)	20 (7.0)	0	29 (7.7)	1 (0.3)	21 (5.5)	0
Constipation	3 (3.3)	0	10 (10.6)	1 (1.1)	25 (8.8)	0	37 (12.9)	1 (0.3)	28 (7.4)	0	47 (12.3)	2 (0.5)

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported in the 'alpelisib' column.
A participant with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A participant with multiple adverse events is counted only once in the total row.
MedDRA version 27.1, CTCAE version 4.03

Treatment-related adverse events

During the double-blind period of Study C2303, the proportion of participants who experienced at least one treatment-related AE was higher in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (97.8% vs 58.5%, respectively). The incidence of grade ≥3 treatment-related AEs was also higher in the alpelisib arm (65.2% vs 12.8%).

The most common treatment-related AEs (>20%) in the alpelisib plus fulvestrant arm (vs placebo) were hyperglycaemia (72.8% vs 11.7%), nausea (39.1% vs 5.3%), diarrhoea (35.9% vs 8.5%), rash (29.3% vs 0%) and decreased appetite (25.0% vs 2.1%). In the placebo and fulvestrant arm, no treatment-related AEs were reported in >15% of participants.

The most common grade ≥ 3 treatment-related AEs (>5%) in the alpelisib + fulvestrant arm (vs placebo) were: hyperglycaemia (32.6% vs 0%), rash (13.0% vs 0%), rash maculo-papular (7.6% vs 0%) and weight decreased (5.4% vs 0%). No grade ≥ 3 treatment-related AEs occurred in >5% of participants in the placebo arm.

In the pooled safety set, all grades treatment-related AEs with >20% frequency and grade ≥ 3 treatment-related AEs with >5% frequency were consistent with those observed in the C2303 study.

Table 38 Treatment-related adverse events by preferred term (>10% participants in any group) and maximum grade (Safety Set)

	C2303				C2301 (SOLAR-1)				Pool			
	Alpelisib + Fluv N=92		Placebo + Fluv N=94		Alpelisib + Fluv N=284		Placebo + Fluv N=287		Alpelisib + Fluv N=376		Placebo + Fluv N=381	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Number of participants with at least one event	90 (97.8)	60 (65.2)	55 (58.5)	12 (12.8)	265 (93.3)	192 (67.6)	184 (64.1)	34 (11.8)	355 (94.4)	252 (67.0)	239 (62.7)	46 (12.1)
Hyperglycaemia	67 (72.8)	30 (32.6)	11 (11.7)	0	174 (61.3)	97 (34.2)	16 (5.6)	0	241 (64.1)	127 (33.8)	27 (7.1)	0
Diarrhoea	33 (35.9)	2 (2.2)	8 (8.5)	0	116 (40.8)	16 (5.6)	21 (7.3)	1 (0.3)	149 (39.6)	18 (4.8)	29 (7.6)	1 (0.3)
Nausea	36 (39.1)	1 (1.1)	5 (5.3)	0	105 (37.0)	5 (1.8)	41 (14.3)	0	141 (37.5)	6 (1.6)	46 (12.1)	0
Rash	27 (29.3)	12 (13.0)	0	0	88 (31.0)	27 (9.5)	13 (4.5)	1 (0.3)	115 (30.6)	39 (10.4)	13 (3.4)	1 (0.3)
Decreased appetite	23 (25.0)	4 (4.3)	2 (2.1)	0	83 (29.2)	1 (0.4)	13 (4.5)	0	106 (28.2)	5 (1.3)	15 (3.9)	0
Fatigue	11 (12.0)	0	4 (4.3)	0	62 (21.8)	8 (2.8)	33 (11.5)	0	73 (19.4)	8 (2.1)	37 (9.7)	0
Stomatitis	14 (15.2)	4 (4.3)	1 (1.1)	0	59 (20.8)	7 (2.5)	11 (3.8)	0	73 (19.4)	11 (2.9)	12 (3.1)	0
Vomiting	13 (14.1)	0	0	0	54 (19.0)	1 (0.4)	10 (3.5)	0	67 (17.8)	1 (0.3)	10 (2.6)	0
Asthenia	18 (19.6)	1 (1.1)	6 (6.4)	0	45 (15.8)	6 (2.1)	18 (6.3)	0	63 (16.8)	7 (1.9)	24 (6.3)	0
Mucosal inflammation	16 (17.4)	3 (3.3)	0	0	40 (14.1)	4 (1.4)	1 (0.3)	0	56 (14.9)	7 (1.9)	1 (0.3)	0
Weight decreased	8 (8.7)	5 (5.4)	0	0	46 (16.2)	8 (2.8)	3 (1.0)	0	54 (14.4)	13 (3.5)	3 (0.8)	0
Rash maculo-papular	10 (10.9)	7 (7.6)	0	0	40 (14.1)	25 (8.8)	4 (1.4)	0	50 (13.3)	32 (8.5)	4 (1.0)	0
Dysgeusia	8 (8.7)	0	0	0	35 (12.3)	0	7 (2.4)	0	43 (11.4)	0	7 (1.8)	0
Pruritus	5 (5.4)	1 (1.1)	0	0	38 (13.4)	2 (0.7)	9 (3.1)	0	43 (11.4)	3 (0.8)	9 (2.4)	0
Alopecia	5 (5.4)	0	0	0	36 (12.7)	0	3 (1.0)	0	41 (10.9)	0	3 (0.8)	0
Dry skin	3 (3.3)	0	2 (2.1)	0	31 (10.9)	0	4 (1.4)	0	34 (9.0)	0	6 (1.6)	0

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported in the 'alpelisib' column.
A participant with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A participant with multiple adverse events is counted only once in the total row.
MedDRA version 27.1, CTCAE version 4.03

Serious adverse event/deaths/other significant events

Serious adverse events

Within the double-blind period of study C2303, the most commonly reported SAEs (>2% of participants) in the alpelisib and fulvestrant arm in comparison with the control arm were: hyperglycaemia, acute kidney injury, decreased appetite, diarrhoea, and rash. In the placebo and fulvestrant arm, the only SAE reported was physical health deterioration. The proportion of SAE considered to be treatment-related was higher in the alpelisib and fulvestrant arm (13.0% vs 2.1%). In the alpelisib and fulvestrant arm, the most common treatment-related SAE reported were hyperglycaemia (4.3%), diarrhoea (2.2%) and acute kidney injury (2.2%). In contrast, only two treatment-related SAEs were reported in the placebo arm: one case of pulmonary embolism and one of pneumonia.

The percentage of participants experiencing at least one SAE in the alpelisib arm was lower in Study C2303 than in Study C2301 (SOLAR-1) (22.8% vs 38.7%, respectively). Even though a similar pattern of SAEs was observed between C2301 (SOLAR-1) and C2303 study, the incidence of certain SAEs, particularly hyperglycaemia and osteonecrosis of the jaw, was higher in Study C2301 compared with Study C2303.

Table 39 Serious adverse events by preferred term (>=1% participant in any group in the pooled safety set) and maximum (Safety Set)

	C2303				C2301				Pool			
	Alpelisib +Fluv N=92		Placebo +Fluv N=94		Alpelisib + Fluv N=284		Placebo + Fluv N=287		Alpelisib + Fluv N=376		Placebo + Fluv N=381	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Number of participants with at least one event	21 (22.8)	19 (20.7)	18 (19.1)	14 (14.9)	110 (38.7)	93 (32.7)	54 (18.8)	48 (16.7)	131 (34.8)	112 (29.8)	72 (18.9)	62 (16.3)
Hyperglycaemia	4 (4.3)	4 (4.3)	0	0	28 (9.9)	25 (8.8)	0	0	32 (8.5)	29 (7.7)	0	0
Diarrhoea	2 (2.2)	1 (1.1)	0	0	9 (3.2)	5 (1.8)	0	0	11 (2.9)	6 (1.6)	0	0
Osteonecrosis of jaw	1 (1.1)	1 (1.1)	0	0	9 (3.2)	7 (2.5)	2 (0.7)	2 (0.7)	10 (2.7)	8 (2.1)	2 (0.5)	2 (0.5)
Acute kidney injury	2 (2.2)	2 (2.2)	0	0	6 (2.1)	4 (1.4)	1 (0.3)	1 (0.3)	8 (2.1)	6 (1.6)	1 (0.3)	1 (0.3)
Abdominal pain	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	6 (2.1)	4 (1.4)	2 (0.7)	1 (0.3)	7 (1.9)	5 (1.3)	3 (0.8)	2 (0.5)
Rash	2 (2.2)	2 (2.2)	0	0	5 (1.8)	4 (1.4)	0	0	7 (1.9)	6 (1.6)	0	0
Anaemia	0	0	0	0	6 (2.1)	4 (1.4)	0	0	6 (1.6)	4 (1.1)	0	0
Decreased appetite	2 (2.2)	1 (1.1)	0	0	3 (1.1)	0	0	0	5 (1.3)	1 (0.3)	0	0
Nausea	0	0	0	0	5 (1.8)	4 (1.4)	2 (0.7)	1 (0.3)	5 (1.3)	4 (1.1)	2 (0.5)	1 (0.3)
Vomiting	0	0	0	0	5 (1.8)	2 (0.7)	3 (1.0)	1 (0.3)	5 (1.3)	2 (0.5)	3 (0.8)	1 (0.3)
Dyspnoea	0	0	0	0	4 (1.4)	3 (1.1)	4 (1.4)	4 (1.4)	4 (1.1)	3 (0.8)	4 (1.0)	4 (1.0)
Hypokalaemia	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	3 (1.1)	3 (1.1)	1 (0.3)	0	4 (1.1)	4 (1.1)	2 (0.5)	1 (0.3)
Pleural effusion	0	0	0	0	4 (1.4)	4 (1.4)	5 (1.7)	4 (1.4)	4 (1.1)	4 (1.1)	5 (1.3)	4 (1.0)
Pneumonia	1 (1.1)	1 (1.1)	1 (1.1)	0	3 (1.1)	3 (1.1)	6 (2.1)	5 (1.7)	4 (1.1)	4 (1.1)	7 (1.8)	5 (1.3)
Pulmonary embolism	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	3 (1.1)	3 (1.1)	3 (1.0)	2 (0.7)	4 (1.1)	4 (1.1)	4 (1.0)	3 (0.8)
Pyrexia	0	0	0	0	4 (1.4)	0	0	0	4 (1.1)	0	0	0
Stomatitis	0	0	0	0	4 (1.4)	2 (0.7)	0	0	4 (1.1)	2 (0.5)	0	0
Back pain	1 (1.1)	0	0	0	2 (0.7)	2 (0.7)	4 (1.4)	3 (1.0)	3 (0.8)	2 (0.5)	4 (1.0)	3 (0.8)
Dehydration	0	0	1 (1.1)	1 (1.1)	3 (1.1)	1 (0.4)	3 (1.0)	3 (1.0)	3 (0.8)	1 (0.3)	4 (1.0)	4 (1.0)

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported in the 'alpelisib' column.

A participant with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A participant with multiple adverse events is counted only once in the total row.

MedDRA version 27.1, CTCAE version 4.03

Deaths

All deaths in Study C2303

Up to the data cut-off date, out of the 60 deaths that occurred in Study C2303 in total, 23 deaths (25.0%) occurred in the alpelisib plus fulvestrant arm and 37 deaths (39.4%) in the placebo plus fulvestrant arm. Among the 34 participants who crossed over from placebo to alpelisib, 15 deaths (44.1%) were reported.

In both treatment arms, the most frequent cause of death was disease progression (study indication). Deaths due to causes other than disease progression occurred in 3 participants (3.3%) in the alpelisib arm and 8 participants (8.5%) in the placebo arm.

Among the crossover population, disease progression was also the most common cause of death (11 of 15 deaths; 32.4%). Four deaths were attributed to causes other than the underlying malignancy: general physical health deterioration, respiratory tract infection, sepsis, and hepatic encephalopathy.

Table 40 All deaths, by system organ class and preferred term in Study C2303 (Safety Set)

		All-participants _ _	
Primary system organ class Primary reason (preferred term)	**Alpelisib + Fulvestrant N=92 n (%)**	**Cross-over N=34 n (%)**	**Placebo + Fulvestrant N=94 n (%)**
Number of participants who died	23 (25.0)	15 (44.1)	37 (39.4)
Study Indication	20 (21.7)	11 (32.4)	29 (30.9)
Other	3 (3.3)	4 (11.8)	8 (8.5)
Cardiac disorders	0	0	1 (1.1)
Cardiac failure	0	0	1 (1.1)
General disorders and administration site conditions	0	1 (2.9)	1 (1.1)
General physical health deterioration	0	1 (2.9)	1 (1.1)
Infections and infestations	1 (1.1)	2 (5.9)	2 (2.1)
Pneumonia	1 (1.1)	0	0
Respiratory tract infection	0	1 (2.9)	1 (1.1)
Sepsis	0	1 (2.9)	1 (1.1)
Injury, poisoning and procedural complications	0	0	1 (1.1)
Respiratory tract procedural complication	0	0	1 (1.1)
Nervous system disorders	0	0	1 (1.1)
Ischaemic stroke	0	0	1 (1.1)
Primary reason: Other (not coded)	0	1 (2.9)	1 (1.1)
Reported term:Hepatic Encephelopathy	0	1 (2.9)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (1.1)	0	1 (1.1)
Pulmonary embolism	1 (1.1)	0	0
Respiratory failure	0	0	1 (1.1)
Vascular disorders	1 (1.1)	0	0
Hypovolaemic shock	1 (1.1)	0	0

N for cross-over includes only those participants who crossed over to open-label alpelisib + fulvestrant arm.

On treatment deaths in Study C2303

During the double-blind period of C2303 Study, 5 participants (5.4%) died in the alpelisib plus fulvestrant arm and 6 (6.4%) died in the placebo and fulvestrant arm. Breast cancer was the cause of death in 2 participants (2.2%) in the alpelisib arm and 4 participants (4.3%) in the placebo arm.

In the alpelsib + fulvestrant arm, the other causes of death were one hypovolemic shock, one pneumonia and one pulmonary embolism (1.1% each). The hypovolemic shock occurred in the context of diarrhoea and sepsis and was assessed by the investigator as related to study treatment. The remaining events (pneumonia and pulmonary embolism) were considered not related to the study treatment by the investigators.

In the cross-over population, death due to hepatic encephalopathy was considered as on-treatment death. However, no information was provided for the other (14) deaths as on-treatment or not.

Deaths in pooled safety set

In the pooled safety population, a total of 183 participants (48.7%) died in the alpelisib plus fulvestrant arm and 205 participants (53.8%) died in the placebo plus fulvestrant arm.

The number of on-treatment deaths was 14 (3.7%) in the alpelisib arm and 18 (4.7%) in the placebo arm. Disease progression was the cause of death in 9 participants (2.4%) in the alpelisib plus fulvestrant arm and 18 participants (4.7%) in the placebo arm.

Table 41 On-treatment deaths (Pooled Safety Set)

	C2303		C2301		Pool	
Category Preferred term	**Alpelisib +Fulv N=92 n(%)**	**Placebo +Fulv N=94 n(%)**	**Alpelisib +Fulv N=284 n(%)**	**Placebo +Fulv N=287 n(%)**	**Alpelisib +Fulv N=376 n(%)**	**Placebo +Fulv N=381 n(%)**
Number of participants who died	5 (5.4)	6 (6.4)	9 (3.2)	12 (4.2)	14 (3.7)	18 (4.7)
Primary reason: Study indication (breast cancer)	2 (2.2)	4 (4.3)	7 (2.5)	9 (3.1)	9 (2.4)	13 (3.4)
Primary reason: Other	3 (3.3)	2 (2.1)	2 (0.7)	3 (1.0)	5 (1.3)	5 (1.3)
Cardio-respiratory arrest	0	0	1 (0.4)	0	1 (0.3)	0
Gastrointestinal haemorrhage	0	0	0	1 (0.3)	0	1 (0.3)
Hypovolaemic shock	1 (1.1)	0	0	0	1 (0.3)	0
Pneumonia	1 (1.1)	0	0	1 (0.3)	1 (0.3)	1 (0.3)
Pulmonary embolism	1 (1.1)	0	0	0	1 (0.3)	0
Respiratory failure	0	1 (1.1)	0	0	0	1 (0.3)
Respiratory tract procedural complication	0	1 (1.1)	0	0	0	1 (0.3)
Second primary malignancy	0	0	1 (0.4)	0	1 (0.3)	0
Septic shock	0	0	0	1 (0.3)	0	1 (0.3)

Numbers (n) represent counts of participants.

A participant may have more than one SAE with fatal outcome.

MedDRA version 27.1.

Adverse events of special interest

The predefined AESIs for Study C2303 were the same as those identified in Study C2301 (SOLAR-1), with the addition of osteonecrosis of the jaw. The AESIs included:

- Hyperglycaemia
- Gastrointestinal toxicity: Including nausea, vomiting and diarrhoea
- Rash
- Hypersensitivity and anaphylactic reaction
- Pancreatitis
- Osteonecrosis of the jaw (ONJ)
- Pneumonitis
- Severe cutaneous reactions

During Study C2303, the AESIs that occurred more frequently in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm were:

- Gastrointestinal toxicity: 70.7% vs 23.4%
- Hyperglycaemia: 72.8% vs 17.0%
- Rash: 44.6% vs 2.1%
- Hypersensitivity and anaphylactic reaction: 9.8% vs 1.1%

Pancreatitis and osteonecrosis of the jaw were slightly higher in the alpelisib and fulvestrant arm in comparison with the placebo arm (4.3% vs 2.2% for pancreatitis and 2.2% vs 1.1% in osteonecrosis of the jaw). Pneumonitis and severe cutaneous reactions were reported similarly in both arms.

The pooled safety population analysis of AESIs showed similar differences in AESIs as observed in Study C2303, but in some cases grade ≥3 AESIs were observed with a higher percentage in C2301 (SOLAR-1) study than C2303.

Table 42 Overview of AESIs

	C2303				C2301				Pool			
	Alpelisib + Fluv N=92		Placebo + Fluv N=94		Alpelisib + Fluv N=284		Placebo + Fluv N=287		Alpelisib + Fluv N=376		Placebo + Fluv N=381	
Safety topic	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
GI toxicity (Nausea Vomiting Diarrhea)	65 (70.7)	3 (3.3)	22 (23.4)	0	219 (77.1)	28 (9.9)	102 (35.5)	4 (1.4)	284 (75.5)	31 (8.2)	124 (32.5)	4 (1.0)
Hyperglycaemia	67 (72.8)	30 (32.6)	16 (17.0)	0	191 (67.3)	111 (39.1)	29 (10.1)	3 (1.0)	258 (68.6)	141 (37.5)	45 (11.8)	3 (0.8)
Rash	41 (44.6)	21 (22.8)	2 (2.1)	0	154 (54.2)	57 (20.1)	27 (9.4)	1 (0.3)	195 (51.9)	78 (20.7)	29 (7.6)	1 (0.3)
Hypersensitivity and anaphylactic reaction	9 (9.8)	1 (1.1)	1 (1.1)	0	50 (17.6)	6 (2.1)	16 (5.6)	1 (0.3)	59 (15.7)	7 (1.9)	17 (4.5)	1 (0.3)
Pancreatitis	4 (4.3)	2 (2.2)	3 (3.2)	3 (3.2)	24 (8.5)	18 (6.3)	18 (6.3)	15 (5.2)	28 (7.4)	20 (5.3)	21 (5.5)	18 (4.7)
Osteonecrosis of jaw	2 (2.2)	1 (1.1)	0	0	17 (6.0)	8 (2.8)	5 (1.7)	3 (1.0)	19 (5.1)	9 (2.4)	5 (1.3)	3 (0.8)
Pneumonitis	1 (1.1)	1 (1.1)	3 (3.2)	3 (3.2)	5 (1.8)	1 (0.4)	1 (0.3)	1 (0.3)	6 (1.6)	2 (0.5)	4 (1.0)	4 (1.0)
Severe Cutaneous Reactions	1 (1.1)	1 (1.1)	0	0	4 (1.4)	3 (1.1)	0	0	5 (1.3)	4 (1.1)	0	0

Gastrointestinal toxicity

In Study C2303, gastrointestinal toxicity, including nausea, vomiting and diarrhoea, was reported more frequently in the alpelisib plus fulvestrant arm than in the placebo plus fulvestrant arm (70.7% vs 23.4%, respectively). The overall incidence of gastrointestinal toxicity in the alpelisib arm was lower in Study C2303 compared with Study C2301 (SOLAR-1). There was no reported cases of diarrhoea of Grade 4. Grade 2 and 3 diarrhoea events were reported in 18.9% and 6.1% of patients (n=94), respectively, with a median time to onset of grade ≥2 diarrhoea of 49.5 days (range: 1 to 1 731 days). In the pooled safety dataset, dose reductions of alpelisib were required in 4.8% of patients and 2.7% of patients discontinued alpelisib treatment due to diarrhoea. In the 217 patients who experienced diarrhoea, antidiarrhoeal medications (e.g. loperamide) were required to manage symptoms in 62.2% (135/217).

Similarly, the frequency of grade ≥3 gastrointestinal toxicity AESIs and gastrointestinal-related SAEs in the alpelisib arm was higher in Study C2301 (SOLAR-1) than in Study C2303, indicating a more favourable gastrointestinal safety profile in the C2303 population.

Antiemetics (e.g. ondansetron) and antidiarrhoeal medicinal products (e.g. loperamide) were used in 40/197 (20.3%) and 135/217 (62.2%) patients, respectively, to manage symptoms.

Table 43 Incidence of gastrointestinal toxicity (AESI)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	65 (70.7) [60.2- 79.7]	22 (23.4) [15.3- 33.3]	219 (77.1) [71.8- 81.9]	102 (35.5) [30.0- 41.4]	284 (75.5) [70.9- 79.8]	124 (32.5) [27.9- 37.5]
Maximum grade						
Grade 2 AEs	26 (28.3)	7 (7.4)	80 (28.2)	31 (10.8)	106 (28.2)	38 (10.0)
Grade 3 AEs	3 (3.3)	0	28 (9.9)	4 (1.4)	31 (8.2)	4 (1.0)
Treatment-related AEs	54 (58.7)	13 (13.8)	173 (60.9)	58 (20.2)	227 (60.4)	71 (18.6)
SAEs	2 (2.2)	0	13 (4.6)	4 (1.4)	15 (4.0)	4 (1.0)

Hyperglycaemia

In Study C2303, hyperglycaemia AESIs were reported more frequently in the alpelisib plus fulvestrant arm than in the placebo plus fulvestrant arm (72.8% vs 17.0%, respectively). In the alpelisib arm, grade 3 hyperglycaemia occurred in 30.4% of participants and grade 4 hyperglycaemia in 2.2%.

SAEs of hyperglycaemia occurred only in the alpelisib plus fulvestrant arm. The frequency in Study C2303 was 4.3%, which was lower than the incidence observed in Study C2301 (10.9%).

Baseline diabetic and pre-diabetic status, baseline BMI ≥30 and baseline age ≥75 years have been found to be risk factors for hyperglycaemia in patients treated with alpelisib. These risk factors were present in 72.9% of patients with any grade of hyperglycaemia and in 83% of patients with grade 3 or 4 hyperglycaemia. In the pooled safety dataset, hyperglycaemia occurred more frequently in patients who were diabetic (1 out of 18 patients [5.6%] with grade 1-2, and 15 out of 18 patients [83.3%] with grade 3-4), pre-diabetic (55 out of 192 patients [28.6%] with grade 1-2, and 91 out of 192 patients [47.4%] with grade 3-4), had BMI ≥30 at screening (21 out of 91 patients [23.1%] with grade 1-2, and 47 out of 91 patients [51.6%] with grade 3-4) or ≥75 years of age (10 out of 46 patients [21.7%] with grade 1-2, and 22 out of 46 patients [47.8%] with grade 3-4).

In the 258 patients with hyperglycaemia, 86% (222/258) were managed with antidiabetic medication, and 74.4% (192/258) reported use of metformin (single agent or in combination with other antidiabetic medication). Oral antidiabetic medication was used in 204 patients. Out of these 204 patients, 19 (9.3%) discontinued study treatment due to hyperglycaemia. Concomitant insulin medication was used in 76 patients; of these 15 (19.7%) discontinued study treatment due to hyperglycaemia. Out of 206 patients with grade ≥2 hyperglycaemia, 195 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=180), 95.0% (n=76) had FPG levels that returned to baseline.

No cases of ketoacidosis or hyperglycaemic hyperosmolar nonketotic syndrome (HHNS) were reported in Study C2303.

Table 44 Incidence of hyperglycaemia (AESI)

	___C2303___		**___C2301___**		**___Pool___**	
	Alpelisib + Fulv N=92 n (%) 95% CI	**Placebo + Fulv N=94 n (%) 95% CI**	**Alpelisib + Fulv N=284 n (%) 95% CI**	**Placebo + Fulv N=287 n (%) 95% CI**	**Alpelisib + Fulv N=376 n (%) 95% CI**	**Placebo + Fulv N=381 n (%) 95% CI**
Number of participants with at least one event	67 (72.8)	16 (17.0)	191 (67.3)	29 (10.1)	258 (68.6)	45 (11.8)
	[62.6-81.6]	[10.1-26.2]	[61.5-72.7]	[6.9-14.2]	[63.7-73.3]	[8.7-15.5]
Maximum grade						
Grade 2 AEs	20 (21.7)	1 (1.1)	45 (15.8)	6 (2.1)	65 (17.3)	7 (1.8)
Grade 3 AEs	28 (30.4)	0	98 (34.5)	2 (0.7)	126 (33.5)	2 (0.5)
Grade 4 AEs	2 (2.2)	0	13 (4.6)	1 (0.3)	15 (4.0)	1 (0.3)
Treatment-related AEs	67 (72.8)	16 (17.0)	179 (63.0)	17 (5.9)	246 (65.4)	33 (8.7)
SAEs	4 (4.3)	0	31 (10.9)	0	35 (9.3)	0
Action taken						
Permanently discontinued	3 (3.3)	0	20 (7.0)	0	23 (6.1)	0
Dose adjusted	19 (20.7)	0	83 (29.2)	2 (0.7)	102 (27.1)	2 (0.5)
Temporarily interrupted	29 (31.5)	0	76 (26.8)	1 (0.3)	105 (27.9)	1 (0.3)
None/NA/Unknown	66 (71.7)	16 (17.0)	170 (59.9)	28 (9.8)	236 (62.8)	44 (11.5)
Medication or therapy taken	57 (62.0)	7 (7.4)	165 (58.1)	13 (4.5)	222 (59.0)	20 (5.2)
AE outcome						
Recovered/resolved	53 (57.6)	10 (10.6)	174 (61.3)	23 (8.0)	227 (60.4)	33 (8.7)

Recovering/resolving	6 (6.5)	2 (2.1)	9 (3.2)	1 (0.3)	15 (4.0)	3 (0.8)
Not recovered/not resolved	16 (17.4)	4 (4.3)	39 (13.7)	6 (2.1)	55 (14.6)	10 (2.6)
Recovered/resolved with sequelae	1 (1.1)	0	6 (2.1)	1 (0.3)	7 (1.9)	1 (0.3)
Unknown	0	0	3 (1.1)	1 (0.3)	3 (0.8)	1 (0.3)

Rash

In Study C2303, AESIs of rash were reported more frequently in participants treated with alpelisib plus fulvestrant compared with those receiving placebo plus fulvestrant (44.6% vs 2.1%, respectively). The most common PTs in the alpelisib arm were rash (30.4% vs 1.1%) and maculopapular rash (10.9% vs 0%). Most rash events in the alpelisib group were grade 3, and no grade 4 events were reported.

In the pooled safety set, rash occurred more frequently in the alpelisib plus fulvestrant arm (51.9%) than in the placebo arm (7.6%). The majority of these events were grade 3 (20.7% vs 0.3%, respectively), with a median time to first onset of 12 days (range: 2 days to 220 days). In study C2301 the frequency of grade 2 and 3 AEs were similar to C2303.

Among patients who received prophylactic antirash treatment including antihistamines, rash was reported less frequently than in the overall population; 28.9% vs 51.9% for all grades, 14.1% vs 20.7% for grade 3, and 4.4% vs 5.1% for rash leading to the permanent discontinuation of alpesilib.

Table 45 Incidence of rash (AESI)

	___C2303___		___C2301___		___Pool___	
	Alpelisib + Fulv N=92 n (%) 95% CI	**Placebo + Fulv N=94 n (%) 95% CI**	**Alpelisib + Fulv N=284 n (%) 95% CI**	**Placebo + Fulv N=287 n (%) 95% CI**	**Alpelisib + Fulv N=376 n (%) 95% CI**	**Placebo + Fulv N=381 n (%) 95% CI**
Number of participants with at least one event	41 (44.6) [34.2- 55.3]	2 (2.1) [0.3- 7.5]	154 (54.2) [48.2- 60.1]	27 (9.4) [6.3- 13.4]	195 (51.9) [46.7- 57.0]	29 (7.6) [5.2- 10.7]
Maximum grade						
Grade 2 AEs	10 (10.9)	0	39 (13.7)	3 (1.0)	49 (13.0)	3 (0.8)
Grade 3 AEs	21 (22.8)	0	57 (20.1)	1 (0.3)	78 (20.7)	1 (0.3)
Treatment-related AEs	39 (42.4)	1 (1.1)	139 (48.9)	17 (5.9)	178 (47.3)	18 (4.7)
SAEs	2 (2.2)	0	10 (3.5)	0	12 (3.2)	0
Action taken						
Permanently discontinued	7 (7.6)	0	12 (4.2)	0	19 (5.1)	0
Dose adjusted	6 (6.5)	0	26 (9.2)	0	32 (8.5)	0
Temporarily interrupted	22 (23.9)	0	62 (21.8)	1 (0.3)	84 (22.3)	1 (0.3)
None/NA/Unknown	39 (42.4)	2 (2.1)	126 (44.4)	27 (9.4)	165 (43.9)	29 (7.6)
Medication or therapy taken	35 (38.0)	0	128 (45.1)	16 (5.6)	163 (43.4)	16 (4.2)
AE outcome						
Recovered/resolved	37 (40.2)	0	146 (51.4)	21 (7.3)	183 (48.7)	21 (5.5)
Recovering/resolving	1 (1.1)	1 (1.1)	3 (1.1)	1 (0.3)	4 (1.1)	2 (0.5)
Not recovered/not resolved	4 (4.3)	1 (1.1)	10 (3.5)	7 (2.4)	14 (3.7)	8 (2.1)
Unknown	1 (1.1)	0	2 (0.7)	0	3 (0.8)	0

Hypersensitivity and anaphylactic reactions

In Study C2303, hypersensitivity and anaphylactic reactions were reported more frequently in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (9.8% vs 1.1%, respectively). Only one participant in the alpelisib arm experienced a grade 3 event. No hypersensitivity-related SAEs were reported in this study.

A higher frequency of hypersensitivity-related AEs was observed in Study C2301 (SOLAR-1), where 50 participants (17.6%) in the alpelisib arm experienced such events. Among these, 6 participants reported hypersensitivity-related SAEs.

Table 46 Incidence of Hypersensitivity and anaphylactic reactions (AESI)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	9 (9.8) [4.6- 17.8]	1 (1.1) [0.0- 5.8]	50 (17.6) [13.4- 22.5]	16 (5.6) [3.2- 8.9]	59 (15.7) [12.2- 19.8]	17 (4.5) [2.6- 7.0]
Maximum grade						
Grade 2 AEs	2 (2.2)	0	16 (5.6)	4 (1.4)	18 (4.8)	4 (1.0)
Grade 3 AEs	1 (1.1)	0	5 (1.8)	1 (0.3)	6 (1.6)	1 (0.3)
Grade 4 AEs	0	0	1 (0.4)	0	1 (0.3)	0
Treatment-related AEs	5 (5.4)	1 (1.1)	23 (8.1)	6 (2.1)	28 (7.4)	7 (1.8)
SAEs	0	0	6 (2.1)	0	6 (1.6)	0

Pancreatitis

In Study C2303, AESIs related to pancreatitis were reported in 4 participants (4.3%) in the alpelisib plus fulvestrant arm and in 3 participants (3.2%) in the placebo plus fulvestrant arm. All events in the alpelisib arm were laboratory findings of increased lipase, and no cases of acute pancreatitis were reported. Two participants (2.2%) in the alpelisib arm experienced grade 3 events.

In Study C2301 (SOLAR-1), a higher incidence of pancreatitis-related AEs was observed, with 24 participants (8.5%) reporting at least one event. Among these, 14 (4.9%) were grade 3, 4 (1.4%) were grade 4, and 2 (0.7%) were classified as SAEs.

Table 47 Incidence of pancreatitis (AESI)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	4 (4.3) [1.2- 10.8]	3 (3.2) [0.7- 9.0]	24 (8.5) [5.5- 12.3]	18 (6.3) [3.8- 9.7]	28 (7.4) [5.0- 10.6]	21 (5.5) [3.4- 8.3]
Maximum grade						
Grade 2 AEs	0	0	4 (1.4)	0	4 (1.1)	0
Grade 3 AEs	2 (2.2)	2 (2.1)	14 (4.9)	12 (4.2)	16 (4.3)	14 (3.7)
Grade 4 AEs	0	1 (1.1)	4 (1.4)	3 (1.0)	4 (1.1)	4 (1.0)
Treatment-related AEs	3 (3.3)	3 (3.2)	16 (5.6)	12 (4.2)	19 (5.1)	15 (3.9)
SAEs	0	0	2 (0.7)	0	2 (0.5)	0

Pneumonitis

In Study C2303, pneumonitis was reported in one participant (1.1%) in the alpelisib plus fulvestrant arm and in three participants (3.2%) in the placebo plus fulvestrant arm. The event reported in the alpelisib arm was considered treatment-related, classified as a SAE, and led to hospitalisation.

In Study C2301 (SOLAR-1), the frequency and pattern of pneumonitis reports were similar to those observed in Study C2303.

Table 48 Incidence of pneumonitis (AESI)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	1 (1.1) [0.0- 5.9]	3 (3.2) [0.7- 9.0]	5 (1.8) [0.6- 4.1]	1 (0.3) [0.0- 1.9]	6 (1.6) [0.6- 3.4]	4 (1.0) [0.3- 2.7]
Maximum grade						
Grade 2 AEs	0	0	3 (1.1)	0	3 (0.8)	0
Grade 3 AEs	1 (1.1)	3 (3.2)	1 (0.4)	1 (0.3)	2 (0.5)	4 (1.0)
Treatment-related AEs	1 (1.1)	0	4 (1.4)	1 (0.3)	5 (1.3)	1 (0.3)
SAEs	1 (1.1)	2 (2.1)	3 (1.1)	1 (0.3)	4 (1.1)	3 (0.8)

Severe cutaneous reactions

In Study C2303, one severe cutaneous reaction was reported and was classified as Stevens–Johnson syndrome. This event was assessed as a grade 4, treatment-related SAE, and led to hospitalisation. The reaction resolved with appropriate medical management. No severe cutaneous reactions were reported in the placebo plus fulvestrant arm.

In the pooled safety population, 5 participants (1.3%) in the alpelisib plus fulvestrant arm experienced at least one AE classified as a severe cutaneous reaction (2 (0.5%) cases of Stevens-Johnson syndrome (SJS) and 3 (0.8%) cases of erythema multiforme (EM)). No cases meeting this definition were reported in the placebo arm. The four events reported in C2301 study were 3 cases of erythema multiforme in three Japanese participants and one Stevens-Johnsons syndrome.

Table 49 Incidence of severe cutaneous reactions (AESI)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	1 (1.1) [0.0- 5.9]	0 [0.0- 3.8]	4 (1.4) [0.4- 3.6]	0 [0.0- 1.3]	5 (1.3) [0.4- 3.1]	0 [0.0- 1.0]
Maximum grade						
Grade 2 AEs	0	0	1 (0.4)	0	1 (0.3)	0
Grade 3 AEs	0	0	3 (1.1)	0	3 (0.8)	0
Grade 4 AEs	1 (1.1)	0	0	0	1 (0.3)	0
Treatment-related AEs	1 (1.1)	0	4 (1.4)	0	5 (1.3)	0
SAEs	1 (1.1)	0	4 (1.4)	0	5 (1.3)	0

Osteonecrosis of the jaw

In Study C2303, 2 participants (2.2%) in the alpelisib plus fulvestrant arm developed ONJ, while no cases were reported in the placebo plus fulvestrant arm. In both affected participants, exposure to bisphosphonates (prior or concomitant) was documented. In one case, the ONJ event was classified as a SAE.

In Study C2301 (SOLAR-1), ONJ was reported more frequently, with 17 participants (6.0%) experiencing at least one event. Among these, 9 cases (3.2%) were considered SAEs.

Table 50 Incidence of ONJ (AESI)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	2 (2.2) [0.3- 7.6]	0 [0.0- 3.8]	17 (6.0) [3.5- 9.4]	5 (1.7) [0.6- 4.0]	19 (5.1) [3.1- 7.8]	5 (1.3) [0.4- 3.0]
Maximum grade						
Grade 2 AEs	1 (1.1)	0	9 (3.2)	2 (0.7)	10 (2.7)	2 (0.5)
Grade 3 AEs	1 (1.1)	0	8 (2.8)	3 (1.0)	9 (2.4)	3 (0.8)
Treatment-related AEs	0	0	2 (0.7)	0	2 (0.5)	0
SAEs	1 (1.1)	0	9 (3.2)	2 (0.7)	10 (2.7)	2 (0.5)

Adverse drug reaction

The Adverse Drug Reaction (ADR) strategy and selection was applied to determine any new ADRs based upon Study C2303 data in addition to the current ADRs in the CDS. Pooled data from Study C2303 and Study C2301 (SOLAR-1) were used to support the causality assessment and determination of frequency category of identified ADRs.

ADR screening and selection followed a three-step process:

- numerical screening activities to identify candidate ADRs
- review of ADR candidates for causality determination
- generation of an ADR frequency table based on identified ADRs

Numerical screening, applied at preferred term and grouped level from Study C2303 and pooled dataset, was as follows:

- Any AE (MedDRA PT, grouped PTs) with > 5% incidence in alpelisib + fulvestrant arm.
- Any AE (MedDRA PT, grouped PTs) with > 2% difference in AEs incidences between alpelisib + fulvestrant arm vs placebo + fulvestrant.
- For the AEs with no reports in placebo arm: any grade ≥3 AE with incidence ≥1%.
- AEs leading to discontinuation of study treatment if occurrence at least 1% more frequently in alpelisib + fulvestrant arm than in placebo + fulvestrant arm.
- SAEs if occurrence at least 1% more frequently in alpelisib + fulvestrant arm than in placebo + fulvestrant arm.
- Any AEs suspected by the Investigator to be drug related with > 1% incidence in alpelisib + fulvestrant arm.
- Laboratory abnormalities with ≥ 2% difference in incidence between alpelisib + fulvestrant vs placebo + fulvestrant

In addition, any PTs not meeting one of the pre-qualified definitions in the previous step, which occur more frequently in alpelisib + fulvestrant with a sufficient number of events with a 2-sided p-value < 0.1 from Fisher's Exact test were flagged as ADR candidates.

ADR candidates, identified through the numerical screening rule, underwent medical review using the Bradford Hill criteria to assess the plausibility of a causal association between alpelisib and these candidate ADRs. These criteria include event severity, temporal relationship, pharmacological action, and the safety profile of other drugs with similar mechanism of action.

Both the MAH's clinical database and safety database were included in the screening for ADR candidates. The safety database was used as an internal control against the clinical database to identify those reported AEs which had not previously been identified in the clinical database, i.e., ADR candidates arising from the safety database only. These ADR candidates underwent medical review on a case-by-case basis to determine whether they should be added to the ADR candidate list as screened from the clinical database.

Finally, the generation of an ADR frequency table for identified ADRs was based on pooled dataset.

After the evaluation of C2303 study results regarding safety, the MAH did not identify new ADR. However, the MAH stated that the following ADRs had a change in frequency:

- Urinary tract infection: From very common (≥1/10) to common (≥1/100 to <1/10)
- Ketoacidosis: From common (≥1/100 to 1/10) to uncommon (≥1/1000 to <1/100)
- Hypertension: From very common (≥1/10) to common (≥1/100 to <1/10)
- Erythema multiforme: From common (≥1/100 to <1/10) to uncommon (≥1/1000 to <1/100)

ADR and their frequency are presented in Table 51.

Table 51 ADRs observed in Study

	Study C2303		Study C2301		Pool		
	Alpelisib + Fulvestrant N=92		Alpelisib + Fulvestrant N=284		Alpelisib + Fulvestrant N=376		
Adverse drug reaction	**Any grade (%)**	**Grade 3 or 4 (%)**	**Any grade (%)**	**Grade 3 or 4 (%)**	**Any grade (%)**	**Grade 3 or 4 (%)**	**Frequency category Any Grade**
Infections and infestations							
Urinary tract infection[1]	6 (6.5)	0	29 (10.2)	2 (0.7)	35 (9.3)	2 (0.5)*	Common
Blood and lymphatic system disorders							
Anaemia	43 (46.7)	0	129 (45.4)	15 (5.3)	172 (45.7)	15 (4.0)*	Very common
Lymphocyte count decreased	54 (58.7)	5 (5.4)	158 (55.6)	28 (9.9)	212 (56.4)	33 (8.8)	Very common
Platelet count decreased	11 (12.0)	0	42 (14.8)	3 (1.1)	53 (14.1)	3 (0.8)	Very common
Immune system disorders							
Hypersensitivity[2]	1 (1.1)	0	12 (4.2)	2 (0.7)	13 (3.5)	2 (0.5)*	Common
Metabolism and nutrition disorders							
Glucose plasma increased	66 (71.7)	22 (23.9)	225 (79.2)	112 (39.4)	291 (77.4)	134 (35.6)	Very common
Glucose plasma decreased	23 (25.0)	0	78 (27.5)	1 (0.4)	101 (26.9)	1 (0.3)	Very common
Decreased appetite	28 (30.4)	4 (4.3)	105 (37.0)	3 (1.1)	133 (35.4)	7 (1.9)*	Very common
Hypokalaemia	5 (5.4)	0	43 (15.1)	19 (6.7)	48 (12.8)	19 (5.1)	Very common
Hypocalcaemia[3]	10 (10.9)	0	79 (27.8)	6 (2.1)	89 (23.7)	6 (1.6)	Very common
Magnesium decreased	4 (4.3)	1 (1.1)	36 (12.7)	1 (0.4)	40 (10.6)	2 (0.5)	Very common
Dehydration	0	0	10 (3.5)	1 (0.4)	10 (2.7)	1 (0.3)*	Common
Ketoacidosis[4]	0	0	3 (1.1)	3 (1.1)	3 (0.8)	3 (0.8)	Uncommon
Hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) #	Not known	Not known	Not known	Not known	Not known	Not known	Not known
Psychiatric disorders							
Insomnia	6 (6.5)	0	22 (7.7)	0	28 (7.4)	0	Common

Nervous system disorders							
Headache[5]	4 (4.3)	0	56 (19.7)	2 (0.7)	60 (16.0)	2 (0.5)*	Very common
Dysgeusia[6]	8 (8.7)	0	44 (15.5)	1 (0.4)	52 (13.8)	1 (0.3)*	Very common
Eye disorders							
Vision blurred	1 (1.1)	0	15 (5.3)	1 (0.4)	16 (4.3)	1 (0.3)*	Common
Dry eye	0	0	10 (3.5)	0	10 (2.7)	0	Common
Uveitis	Not known	Not known	Not known	Not known	Not known	Not known	Not known
Vascular disorders							
Hypertension	4 (4.3)	0	30 (10.6)	15 (5.3)	34 (9.0)	15 (4.0)	Common
Lymphoedema	3 (3.3)	0	17 (6.0)	0	20 (5.3)	0	Common
Respiratory, thoracic and mediastinal disorders							
Pneumonitis[7]	1 (1.1)	1 (1.1)	5 (1.8)	1 (0.4)	6 (1.6)	2 (0.5)*	Common
Gastrointestinal disorders							
Diarrhoea	47 (51.1)	2 (2.2)	170 (59.9)	21 (7.4)	217 (57.7)	23 (6.1)*	Very common
Nausea	41 (44.6)	1 (1.1)	133 (46.8)	8 (2.8)	174 (46.3)	9 (2.4)*	Very common
Stomatitis[8]	15 (16.3)	4 (4.3)	87 (30.6)	7 (2.5)	102 (27.1)	11 (2.9)*	Very common
Vomiting	17 (18.5)	0	84 (29.6)	2 (0.7)	101 (26.9)	2 (0.5)*	Very common
Abdominal pain	10 (10.9)	1 (1.1)	53 (18.7)	4 (1.4)	63 (16.8)	5 (1.3)*	Very common
Dyspepsia	6 (6.5)	1 (1.1)	33 (11.6)	0	39 (10.4)	1 (0.3)*	Very common
Toothache	0	0	13 (4.6)	1 (0.4)	13 (3.5)	1 (0.3)*	Common
Gingivitis	0	0	11 (3.9)	1 (0.4)	11 (2.9)	1 (0.3)*	Common
Gingival pain	1 (1.1)	0	11 (3.9)	0	12 (3.2)	0	Common
Cheilitis	0	0	8 (2.8)	0	8 (2.1)	0	Common
Pancreatitis	0	0	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)	Uncommon
Colitis[#]	Not known	Not known	Not known	Not known	Not known	Not known	Not known
Skin and subcutaneous tissue disorders							
Rash[9]	40 (43.5)	21 (22.8)	148 (52.1)	55 (19.4)	188 (50.0)	76 (20.2) *	Very common

Alopecia	5 (5.4)	0	58 (20.4)	0	63 (16.8)	0	Very common
Pruritus	7 (7.6)	1 (1.1)	54 (19.0)	2 (0.7)	61 (16.2)	3 (0.8) *	Very common
Dry skin[10]	3 (3.3)	0	53 (18.7)	1 (0.4)	56 (14.9)	1 (0.3) *	Very common
Erythema[11]	3 (3.3)	1 (1.1)	19 (6.7)	2 (0.7)	22 (5.9)	3 (0.8) *	Common
Dermatitis[12]	2 (2.2)	0	10 (3.5)	2 (0.7)	12 (3.2)	2 (0.5) *	Common
Palmar-plantar erythrodysaesthesia syndrome	2 (2.2)	0	5 (1.8)	0	7 (1.9)	0	Common
Erythema multiforme	0	0	3 (1.1)	2 (0.7)	3 (0.8)	2 (0.5) *	Uncommon
Stevens-Johnson syndrome	1 (1.1)	1 (1.1)	1 (0.4)	1 (0.4)	2 (0.5)	2 (0.5)	Uncommon
Drug reaction with eosinophilia and systemic symptoms (DRESS)#	Not known	Not known	Not known	Not known	Not known	Not known	Not known
Angioedema#	Not known	Not known	Not known	Not known	Not known	Not known	Not known
Musculoskeletal and connective tissue disorders							
Muscle spasms[13]	2 (2.2)	0	24 (8.5)	0	26 (6.9)	0	Common
Myalgia	3 (3.3)	1 (1.1)	20 (7.0)	1 (0.4)	23 (6.1)	2 (0.5) *	Common
Osteonecrosis of jaw[14]	2 (2.2)	1 (1.1)	17 (6.0)	8 (2.8)	19 (5.1)	9 (2.4) *	Common
Renal and urinary disorders							
Acute kidney injury	5 (5.4)	2 (2.2)	17 (6.0)	6 (2.1)	22 (5.9)	8 (2.1)	Common
General disorders and administration site conditions							
Fatigue[15]	38 (41.3)	4 (4.3)	125 (44.0)	16 (5.6)	163 (43.4)	20 (5.3) *	Very common
Mucosal inflammation	21 (22.8)	3 (3.3)	56 (19.7)	6 (2.1)	77 (20.5)	9 (2.4) *	Very common
Oedema peripheral	8 (8.7)	0	48 (16.9)	0	56 (14.9)	0	Very common
Pyrexia	13 (14.1)	1 (1.1)	48 (16.9)	2 (0.7)	61 (16.2)	3 (0.8)	Very common
Mucosal dryness[16]	8 (8.7)	0	38 (13.4)	1 (0.4)	46 (12.2)	1 (0.3) *	Very common
Oedema[17]	3 (3.3)	0	20 (7.0)	0	23 (6.1)	0	Common
Investigations							
Weight decreased	14 (15.2)	5 (5.4)	80 (28.2)	17 (6.0)	94 (25.0)	22 (5.9) *	Very common
Blood creatinine increased	66 (71.7)	2 (2.2)	193 (68.0)	9 (3.2)	259 (68.9)	11 (2.9)	Very common

Gamma-glutamyltransferase increased	51 (55.4)	15 (16.3)	154 (54.2)	35 (12.3)	205 (54.5)	50 (13.3)	Very common
Alanine aminotransferase increased	51 (55.4)	4 (4.3)	128 (45.1)	13 (4.6)	179 (47.6)	17 (4.5)	Very common
Lipase increased[18]	28 (30.4)	5 (5.4)	123 (43.3)	20 (7.0)	151 (40.2)	25 (6.6)	Very common
Activated partial thromboplastin time (aPTT) prolonged	24 (26.1)	1 (1.1)	68 (23.9)	2 (0.7)	92 (24.5)	3 (0.8) *	Very common
Albumin decreased	6 (6.5)	0	44 (15.5)	1 (0.4)	50 (13.3)	1 (0.3) *	Very common
Glycosylated haemoglobin increased	1 (1.1)	0	9 (3.2)	0	10 (2.7)	0	Common

* 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 Hypocalcaemia: also includes adjusted calcium decreased and blood calcium decreased
4 Ketoacidosis: also includes diabetic ketoacidosis
5 Headache: also includes head discomfort and tension headache
6 Dysgeusia: also includes ageusia, hypogeusia
7 Pneumonitis: also includes interstitial lung disease
8 Stomatitis: also includes aphthous ulcer and mouth ulceration
9 Rash: also includes rash maculopapular, rash macular, rash papular, rash pruritic
10 Dry skin: also includes skin fissures, xerosis, xeroderma
11 Erythema: also includes erythema generalised
12 Dermatitis: also includes dermatitis acneiform
13 Muscle spasms: also includes muscle discomfort
14 Osteonecrosis of jaw: also includes osteonecrosis
15 Fatigue: also includes asthenia
16 Mucosal dryness: also includes dry mouth, vulvovaginal dryness, dry lip
17 Oedema: also includes face swelling, face oedema, eyelid oedema
18 Lipase increased also includes hyperlipasaemia

Laboratory findings

Haematology

During study C2303 haematology abnormalities were more frequent in the alpelisib + fulvestrant arm in comparison with the placebo + fulvestrant arm.

In the pooled safety analysis, the pattern and ranking of haematology abnormalities were consistent with those observed in Study C2303.

Table 52 Worst Post-baseline haematology abnormalities – overall and by maximum CTC grade (Safety Set)

	C2303						C2301						Pool					
	Alpelisib + Fulvestrant N =92			Placebo + Fulvestrant N =94			Alpelisib + Fulvestrant N =284			Placebo + Fulvestrant N =287			Alpelisib + Fulvestrant N =376			Placebo + Fulvestrant N =381		
	All Grds n (%)	Grd 3 n (%)	Grd 4 n (%)	All Grds n (%)	Grd 3 n (%)	Grd 4 n (%)	All Grds n (%)	Grd 3 n (%)	Grd 4 n (%)	All Grds n (%)	Grd 3 n (%)	Grd 4 n (%)	All Grds n (%)	Grd 3 n (%)	Grd 4 n (%)	All Grds n (%)	Grd 3 n (%)	Grd 4 n (%)
Activated partial thromboplastin time (sec), platelet poor plasma - increase	24 (26.1)	1 (1.1)	0	14 (14.9)	2 (2.1)	0	68 (23.9)	2 (0.7)	0	53 (18.5)	2 (0.7)	0	92 (24.5)	3 (0.8)	0	67 (17.6)	4 (1.0)	0
Hemoglobin (g/L), blood - increase	2 (2.2)	0	0	1 (1.1)	0	0	15 (5.3)	1 (0.4)	0	3 (1.0)	0	0	17 (4.5)	1 (0.3)	0	4 (1.0)	0	0
Hemoglobin (g/L), blood - decrease	43 (46.7)	0	0	35 (37.2)	3 (3.2)	0	129 (45.4)	15 (5.3)	0	86 (30.0)	5 (1.7)	0	172 (45.7)	15 (4.0)	0	121 (31.8)	8 (2.1)	0
Leukocytes (10^9/L), blood - increase	0	0	0	0	0	0	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Leukocytes (10^9/L), blood - decrease	30 (32.6)	0	0	28 (29.8)	0	0	82 (28.9)	3 (1.1)	1 (0.4)	91 (31.7)	0	1 (0.3)	112 (29.8)	3 (0.8)	1 (0.3)	119 (31.2)	0	1 (0.3)
Lymphocytes (10^9/L), blood - increase	3 (3.3)	0	0	2 (2.1)	0	0	13 (4.6)	2 (0.7)	0	8 (2.8)	2 (0.7)	0	16 (4.3)	2 (0.5)	0	10 (2.6)	2 (0.5)	0
Lymphocytes (10^9/L), blood - decrease	54 (58.7)	5 (5.4)	0	47 (50.0)	5 (5.3)	0	158 (55.6)	25 (8.8)	3 (1.1)	117 (40.8)	13 (4.5)	0	212 (56.4)	30 (8.0)	3 (0.8)	164 (43.0)	18 (4.7)	0
Neutrophils (10^9/L), blood - decrease	19 (20.7)	0	0	18 (19.1)	0	0	57 (20.1)	7 (2.5)	2 (0.7)	70 (24.4)	4 (1.4)	2 (0.7)	76 (20.2)	7 (1.9)	2 (0.5)	88 (23.1)	4 (1.0)	2 (0.5)
Platelets (10^9/L), blood - decrease	11 (12.0)	0	0	4 (4.3)	0	0	42 (14.8)	2 (0.7)	1 (0.4)	21 (7.3)	2 (0.7)	0	53 (14.1)	2 (0.5)	1 (0.3)	25 (6.6)	2 (0.5)	0
Prothrombin Intl. normalized ratio (RATIO), plasma - increase	10 (10.9)	1 (1.1)	0	8 (8.5)	1 (1.1)	0	53 (18.7)	0	0	51 (17.8)	2 (0.7)	0	63 (16.8)	1 (0.3)	0	59 (15.5)	3 (0.8)	0

Baseline is defined as the last non-missing value on or prior to the start date of study treatment.
Percentage is based on N.
Participants 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 summarised.

Clinical chemistry

In Study C2303, the most frequent clinical chemistry abnormalities in the alpelisib plus fulvestrant arm showing a ≥10% higher incidence compared with the placebo plus fulvestrant arm were, respectively, increased fasting serum/plasma glucose (71.7% vs 30.9%), increased serum/plasma creatinine (71.7% vs 25.5%), increased serum AST (65.2% vs 54.3%), increased serum/plasma creatine kinase (32.6% vs 16.0%), increased serum lipase (30.4% vs 19.1%) and increased serum amylase (25.0% vs 14.9%).

Grade 3 biochemistry abnormalities with a higher frequency of 5% in the alpelisib plus fulvestrant arm and placebo and fulvestrant arm were, respectively, increased fasting plasma/serum glucose (20.7% vs 1.1%), increased serum GGT (12.0% VS 17.0%), increased serum AST (6.5% vs 7.4%) and increased serum ALT (4.3% vs 7.4%). The most common grade 4 clinical chemistry abnormalities in the alpelisib + fulvestrant arm and placebo + fulvestrant arm was respectively, increased serum GGT (4.3% vs 2.1%), increased serum/plasma glucose (3.3% vs 0) and increased serum urate (3.3% vs 2.1%).

In the pooled safety analysis set, the clinical chemistry abnormalities showed a similar pattern as those observed in C2303 study. Abnormalities with a greater difference of 20% between the alpelisib and placebo arm were increased serum/plasma glucose (77.4% vs 33.9%) and increased serum/plasma creatinine (68.9% vs 26.5%). Grade 3 chemistry abnormalities (>10% of participants in any group) in the alpelisib plus fulvestrant group and placebo plus fulvestrant group, respectively, were increased fasting plasma/serum glucose (30.3% vs. 1.0%) and increased serum GGT (11.2% vs.11.3%). The most common grade 4 abnormalities (>1% in either group) in the alpelisib plus fulvestrant group and placebo plus fulvestrant group were, respectively, increased fasting serum/plasma glucose (5.3% vs0.5%), increased serum GGT (2.1% vs 1.8%), increased serum lipase (1.3% vs. 1.6%), increased serum urate (3.5% vs 1.8%) and decreased plasma/serum potassium (1.1% vs 0%).

Liver enzymes

In study C2303 the incidence of ALT and/or AST levels above >3x ULN and >5x ULN were lower in the alpelisib and fulvestrant arm than placebo and fulvestrant. There were not elevations of ALT and/or AST >20x ULN in either of the arms of the clinical trial. No participants in either of the arms met the biochemical definition of Hy's Law.

In the pooled safety set, abnormalities in liver parameters occurred in similar patterns as observed in the C2303 study. One participant in the alpelisib and fulvestrant group met the biochemical criteria for Hy's Law.

Table 53 Number of participants with elevations of liver chemistry tests (Safety Set)

	C2303		**C2301**		**Pool**	
	Alpelisib + Fulvestrant N =92 n (%)	**Placebo + Fulvestrant N=94 n (%)**	**Alpelisib + Fulvestrant N =284 n (%)**	**Placebo + Fulvestrant N=287 n (%)**	**Alpelisib + Fulvestrant N =376 n (%)**	**Placebo + fulvestrant N=381 n (%)**
Worst post-baseline values						
ALT >3x ULN	6 (6.5)	11 (11.7)	25 (8.8)	15 (5.2)	31 (8.2)	26 (6.8)
ALT >5x ULN	4 (4.3)	7 (7.4)	13 (4.6)	7 (2.4)	17 (4.5)	14 (3.7)
ALT >10x ULN	1 (1.1)	1 (1.1)	4 (1.4)	1 (0.3)	5 (1.3)	2 (0.5)
ALT >20x ULN	0	0	3 (1.1)	0	3 (0.8)	0
AST >3x ULN	9 (9.8)	13 (13.8)	25 (8.8)	20 (7.0)	34 (9.0)	33 (8.7)
AST >5x ULN	6 (6.5)	7 (7.4)	11 (3.9)	8 (2.8)	17 (4.5)	15 (3.9)
AST >10x ULN	1 (1.1)	0	5 (1.8)	2 (0.7)	6 (1.6)	2 (0.5)
AST >20x ULN	0	0	3 (1.1)	2 (0.7)	3 (0.8)	2 (0.5)
ALT or AST >3x ULN	11 (12.0)	14 (14.9)	32 (11.3)	25 (8.7)	43 (11.4)	39 (10.2)
ALT or AST >5x ULN	6 (6.5)	10 (10.6)	13 (4.6)	10 (3.5)	19 (5.1)	20 (5.2)
ALT or AST >8x ULN	2 (2.2)	3 (3.2)	7 (2.5)	3 (1.0)	9 (2.4)	6 (1.6)
ALT or AST >10x ULN	1 (1.1)	1 (1.1)	5 (1.8)	2 (0.7)	6 (1.6)	3 (0.8)
ALT or AST >20x ULN	0	0	3 (1.1)	2 (0.7)	3 (0.8)	2 (0.5)

Total bilirubin (TBILI) >2x ULN	0	3 (3.2)	2 (0.7)	3 (1.0)	2 (0.5)	6 (1.6)
Total bilirubin (TBILI) >3x ULN	0	1 (1.1)	0	3 (1.0)	0	4 (1.0)
Combined and concurrent values post-baseline						
ALT and AST <= ULN at baseline						
ALT or AST >3x ULN & TBILI >2x ULN	0	0	0	0	0	0
ALT or AST >3x ULN & TBILI >2x ULN & ALP >=2x ULN	0	0	0	0	0	0
ALT or AST >3x ULN & TBILI >2x ULN & ALP <2x ULN	0	0	0	0	0	0
ALT and AST > ULN at baseline						
Elevated ALT or AST (>3x Baseline value or 8x ULN) & TBILI (>2x Baseline value and 2x ULN)	0	2 (2.1)	1 (0.4)	1 (0.3)	1 (0.3)	3 (0.8)
Elevated ALT or AST (>3x Baseline value or 8x ULN) & TBILI (>2x Baseline value and 2x ULN) & ALP >=2x ULN	0	2 (2.1)	1 (0.4)	1 (0.3)	1 (0.3)	3 (0.8)
Elevated ALT or AST (>3x Baseline value or 8x ULN) & TBILI (>2x Baseline value and 2x ULN) & ALP <2x ULN	0	0	1 (0.4)	0	1 (0.3)	0

Categories are based on worst post-baseline value for any specific parameter. Categories with multiple parameters are based on worst post-baseline value for each parameter.
Worst post-baseline value refers to maximum post-baseline value except for ALP for which it refers to the minimum post-baseline value.
n = number of participants who satisfied the criteria. Percentage is based on N.

Safety in special populations

Subgroup analyses for all AEs and AESIs based on C2303 study and data for the pooled safety set were performed for baseline demographic characteristics, such as race and age, and region. Subgroup analysis by Sex was not performed, since only 2 (2.1%) participants were male.

In Study C2303, renal and hepatic impairment were not specifically evaluated, as previous clinical data had shown that neither mild nor moderate renal impairment and mild, moderate or severe hepatic impairment resulted in clinically relevant alterations in the safety profile of alpelisib, and no dose-adjustment requirements or safety concerns were identified in these populations. However, caution should be used in patients with severe renal impairment, as there is no experience within this population.

Age

Of 376 patients who received alpesilib in combination with fulvestrant in the phase III studies (in the alpelisib plus fulvestrant arm), 157 patients were ≥65 years of age and 46 patients were between 75 and 87 years of age.

In Study C2303, the number of participants aged ≥75 years treated with alpelisib was limited (N=12). Within the alpelisib arm, participants aged ≥65 years showed a lower proportion of grade ≥3 AEs compared with those <65 years. These results were not observed in the pooled safety set, were patients older than 65 years old showed a higher frequency of grade≥ 3 AEs.

When compared with the pooled safety population, Study C2303 showed a lower proportion of grade ≥3 AEs in both the ≥75-year and ≥65-year subgroups within the alpelisib arm.

Table 54 AEs differences by age group (≥65 years vs <65 years and ≥75years vs <75 years) in Study C2303.

≥65 years	**Alpelisib + Fulvestrant N=40**	**Placebo + Fulvestrant N=36**
All AEs, N (%)	40 (100)	32 (88.9)
Grade ≥3, N (%)	27 (67.5)	11 (30.6)
<65 years	**Alpelisib + Fulvestrant N=52**	**Placebo + Fulvestrant N=58**
All AEs, N (%)	52 (100)	49 (84.5)
Grade ≥3, N (%)	38 (73.1)	20 (34.5)
≥75 years	**Alpelisib + Fulvestrant N=12**	**Placebo + Fulvestrant N=10**
All AEs, N (%)	12 (100)	9 (90.0)
Grade ≥3, N (%)	7 (58.3)	4 (40.0)
<75 years	**Alpelisib + Fulvestrant N=80**	**Placebo + Fulvestrant N=84**
All AEs, N (%)	80 (100)	72 (85.7)
Grade ≥3, N (%)	58 (72.5)	27 (32.1)

Table 55 AEs differences by age group (≥65 years vs <65 years and ≥75years vs <75 years) in Polled Safety Set.

≥65 years	**Alpelisib + Fulvestrant N=159**	**Placebo + Fulvestrant N=170**
All AEs, N (%)	156 (99.4)	158 (92.9)
Grade ≥3, N (%)	129 (82.2)	64 (37.6)

<65 years	**Alpelisib + Fulvestrant** **N=219**	**Placebo + Fulvestrant** **N=221**
All AEs, N (%)	218 (99.5)	190 (90.0)
Grade ≥3, N (%)	160 (73.1)	74 (35.1)
≥75 years	**Alpelisib + Fulvestrant** **N=46**	**Placebo + Fulvestrant** **N=49**
All AEs, N (%)	46 (100)	45 (91.8)
Grade ≥3, N (%)	38 (82.6)	16 (32.7)
<75 years	**Alpelisib + Fulvestrant** **N=330**	**Placebo + Fulvestrant** **N=332**
All AEs, N (%)	328 (99.4)	303 (91.3)
Grade ≥3, N (%)	251 (76.1)	122 (36.7)

Differences in AESIs between age subgroups were observed. In Study C2303, within the alpelisib plus fulvestrant arm, AESIs related to gastrointestinal toxicity, rash, and hypersensitivity/anaphylactic reactions were reported more frequently in participants aged <65 years compared with those aged ≥65 years. In contrast, in the pooled safety set, participants treated with alpelisib plus fulvestrant showed higher rates of gastrointestinal toxicity, hyperglycaemia, and rash in both the ≥65-year and ≥75-year subgroup.

Table 56 Overview of AESI (all grades) by age group of Study C2303.

	Alpelisib 300 mg + fulvestrant				Placebo + fulvestrant			
	<65 N=52	≥65 N=40	<75 N=80	≥75 N=12	<65 N=58	≥65 N=36	<75 N=84	≥75 N=10
AESI	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GI toxicity (nausea, vomiting, diarrhea)	38 (73.1)	27 (67.5)	56 (70.0)	9 (75.0)	9 (15.5)	13 (36.1)	18 (21.4)	4 (40.0)
Hyperglycaemia	37 (71.2)	30 (75.0)	58 (72.5)	9 (75.0)	9 (15.5)	7 (19.4)	15 (17.9)	1 (10.0)
Rash	26 (50.0)	15 (37.5)	36 (45.0)	5 (41.7)	1 (1.7)	1 (2.8)	1 (1.2)	1 (10.0)
Hypersensitivity and anaphylactic reaction	8 (15.4)	1 (2.5)	9 (11.3)	0	1 (1.7)	0	1 (1.2)	0
Pancreatitis	3 (5.8)	1 (2.5)	4 (5.0)	0	2 (3.4)	1 (2.8)	3 (3.6)	0
Osteonecrosis of jaw	1 (1.9)	1 (2.5)	2 (2.5)	0	0	0	0	0
Pneumonitis	1 (1.9)	0	1 (1.3)	0	2 (3.4)	1 (2.8)	3 (3.6)	0
Severe cutaneous reactions	1 (1.9)	0	1 (1.3)	0	0	0	0	0

Table 57 Overview of AESI (all grades) by age group of Pooled Safety Set.

	Alpelisib 300 mg + fulvestrant				Placebo + fulvestrant			
	<65 N=219	≥65 N=157	<75 N=330	≥75 N=46	<65 N=211	≥65 N=170	<75 N=332	≥75 N=49
AESI	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GI toxicity (nausea, vomiting, diarrhea)	162 (74.0)	122 (77.7)	245 (74.2)	39 (84.8)	65 (30.8)	59 (34.7)	109 (32.8)	15 (30.6)
Hyperglycaemia	147 (67.1)	111 (70.7)	224 (67.9)	34 (73.9)	24 (11.4)	21 (12.4)	41 (12.3)	4 (8.2)
Rash	110 (50.2)	85 (54.1)	170 (51.5)	25 (54.3)	18 (8.5)	11 (6.5)	26 (7.8)	3 (6.1)
Hypersensitivity and anaphylactic reaction	37 (16.9)	22 (14.0)	57 (17.3)	2 (4.3)	10 (4.7)	7 (4.1)	17 (5.1)	0
Pancreatitis	15 (6.8)	13 (8.3)	26 (7.9)	2 (4.3)	10 (4.7)	11 (6.5)	17 (5.1)	1 (2.0)
Osteonecrosis of jaw	12 (5.5)	7 (4.5)	17 (5.2)	2 (4.3)	1 (0.5)	4 (2.4)	4 (1.2)	4 (8.2)
Pneumonitis	4 (1.8)	2 (1.3)	6 (1.8)	0	3 (1.4)	1 (0.6)	4 (1.2)	0
Severe cutaneous reactions	3 (1.4)	2 (1.3)	5 (1.5)	0	0	0	0	0

Race

In Study C2303, most participants were White, representing 91.3% of the alpelisib plus fulvestrant arm and 88.3% of the placebo plus fulvestrant arm. Only one participant in the alpelisib arm was

Asian. Additionally, 7 participants in the alpelisib arm and 11 participants in the placebo arm were classified as Other.

In contrast, the pooled safety population included a more diverse racial distribution, with White participants accounting for 75.3% of the alpelisib arm and 68.2% of the placebo arm. The second most common racial group was Asian, comprising 16.0% of the alpelisib arm and 17.3% of the placebo arm.

A summary of adverse events by race in the pooled safety set is presented in the table below:

Table 58. AEs by race in the Pooled Safety Set

Asian	**Alpelisib + Fulvestrant N=60**	**Placebo + Fulvestrant N=66**
All AEs, N (%)	59 (98.3)	59 (89.4)
Grade ≥3, N (%)	48 (80.0)	20 (30.3)
American Indian; Alaskan-Native	**Alpelisib + Fulvestrant N=1**	**Placebo + Fulvestrant N=4**
All AEs, N (%)	1 (100)	4 (100)
Grade ≥3, N (%)	0	1 (25)
Black; African American	**Alpelisib + Fulvestrant N=2**	**Placebo + Fulvestrant N=6**
All AEs, N (%)	2 (100)	6 (100)
Grade ≥3, N (%)	1 (50)	2 (33.3)
White	**Alpelisib + Fulvestrant N=2**	**Placebo + Fulvestrant N=6**
All AEs, N (%)	282 (99.6)	239 (91.9)
Grade ≥3, N (%)	220 (77.7)	94 (36.2)
Unknown	**Alpelisib + Fulvestrant N=21**	**Placebo + Fulvestrant N=28**
All AEs, N (%)	21 (100)	25 (89.3)
Grade ≥3, N (%)	13 (61.9)	12 (42.9)
Other	**Alpelisib + Fulvestrant N=9**	**Placebo + Fulvestrant N=17**
All AEs, N (%)	9 (100)	15 (88.2)
Grade ≥3, N (%)	7 (77.8)	9 (52.9)

In the pooled safety set, several AESIs occurred more frequently in Asian participants than in White participants within the alpelisib plus fulvestrant arm. These included rash (77.3% vs 48.1%), hypersensitivity and anaphylactic reactions (30.0% vs 13.1%), pancreatitis (11.7% vs 6.4%), osteonecrosis of the jaw (8.3% vs 4.6%), and severe cutaneous reactions (6.7% vs 0.4%). In the placebo arm, these AESIs also occurred at higher frequencies in Asian participants compared to White participants, although the differences were smaller.

Table 59 AESIs in alpelisib plus fulvestrant arm in the Pooled Safety Set by race

Safety topic	Asian N=60 n(%)	American Indian or Alaska Native N=1 n(%)	Black or African American N=2 n(%)	White N=283 n(%)	Unknown N=21 n(%)	Other N=9 n(%)
GI toxicity (Nausea Vomiting Diarrhea)	43 (71.7)	1 (100)	1 (50.0)	214 (75.6)	19 (90.5)	6 (66.7)
Hyperglycaemia	42 (70.0)	1 (100)	0	196 (69.3)	13 (61.9)	6 (66.7)
Rash	44 (73.3)	0	1 (50.0)	136 (48.1)	11 (52.4)	3 (33.3)
Hypersensitivity and anaphylactic reaction	18 (30.0)	0	0	37 (13.1)	2 (9.5)	2 (22.2)
Pancreatitis	7 (11.7)	0	0	18 (6.4)	3 (14.3)	0
Osteonecrosis of jaw	5 (8.3)	0	0	13 (4.6)	1 (4.8)	0
Pneumonitis	1 (1.7)	0	0	5 (1.8)	0	0
Severe Cutaneous Reactions	4 (6.7)	0	0	1 (0.4)	0	0

Table 60 AESIs in the placebo plus fulvestrant arm in the Pooled Safety Set by race

Safety topic	Asian N=66 n(%)	American Indian or Alaska Native N=4 n(%)	Black or African American N=6 n(%)	White N=260 n(%)	Unknown N=28 n(%)	Other N=17 n(%)
GI toxicity (Nausea Vomiting Diarrhea)	16 (24.2)	2 (50.0)	3 (50.0)	91 (35.0)	10 (35.7)	2 (11.8)
Hyperglycaemia	6 (9.1)	0	1 (16.7)	33 (12.7)	4 (14.3)	1 (5.9)
Rash	15 (22.7)	0	3 (50.0)	9 (3.5)	2 (7.1)	0
Hypersensitivity and anaphylactic reaction	5 (7.6)	0	0	11 (4.2)	0	1 (5.9)
Pancreatitis	4 (6.1)	0	1 (16.7)	14 (5.4)	2 (7.1)	0
Osteonecrosis of jaw	2 (3.0)	0	0	2 (0.8)	0	1 (5.9)
Pneumonitis	0	0	0	3 (1.2)	1 (3.6)	0
Severe Cutaneous Reactions	0	0	0	0	0	0

Region

Study C2303 was conducted in Canada and Europe. Most participants were recruited in Europe, with 89 participants in the alpelisib plus fulvestrant arm and 94 participants in the placebo plus fulvestrant arm. Only three participants in the alpelisib arm were enrolled in North America.

In the pooled safety set, 63.4% of participants were from Europe, 15.9% from Asia, 9.1% from North America, 5.7% from Latin America, and 5.9% were classified as Other, a category that included Australia, Lebanon, and Israel. General AEs and grade ≥3 AEs by geographic region are summarised in the table below.

Table 61 AEs by region in the Pooled Safety Set

Asia	**Alpelisib + Fulvestrant N=56**	**Placebo + Fulvestrant N=64**
All AEs, N (%)	55 (98.2)	57 (89.1)
Grade ≥3, N (%)	44 (78.6)	19 (29.7)
Europe	**Alpelisib + Fulvestrant N=242**	**Placebo + Fulvestrant N=238**
All AEs, N (%)	242 (100)	214 (89.9)
Grade ≥3, N (%)	183 (75.6)	89 (37.4)

Latin America	**Alpelisib + Fulvestrant N=17**	**Placebo + Fulvestrant N=26**
All AEs, N (%)	17 (100)	24 (92.3)
Grade ≥3, N (%)	10 (58.8)	11 (42.3)
North America	**Alpelisib + Fulvestrant N=32**	**Placebo + Fulvestrant N=37**
All AEs, N (%)	31 (96.9)	37 (100)
Grade ≥3, N (%)	27 (84.4)	12 (32.4)
Other	**Alpelisib + Fulvestrant N=29**	**Placebo + Fulvestrant N=16**
All AEs, N (%)	29 (100)	16 (100)
Grade ≥3, N (%)	25 (86.2)	7 (43.8)

When evaluating the AESIs by region, a higher trend of hyperglycaemia, rash, hypersensitivity and anaphylactic reactions, pancreatitis and severe cutaneous reactions was observed in participants from Asia among the alpelisib and fulvestrant arm. GI toxicity in the alpelisib and fulvestrant arm was more frequently observed in participants from North America.

Table 62. AESIs by region in the Pooled Safety Set.

	Alpelisib 300 mg + fulvestrant				Placebo + fulvestrant			
	Europe	North America	Asia	Latin America	Europe	North America	Asia	Latin America
AESI	N=242 n (%)	N=32 n (%)	N=56 n (%)	N=17 n (%)	N=238 n (%)	N=37 n (%)	N=64 n (%)	N=26 n (%)
GI toxicity (nausea, vomiting, diarrhea)	180 (74.4)	29 (90.6)	40 (71.4)	11 (64.7)	76 (31.9)	19 (51.4)	15 (23.4)	6 (23.1)
Hyperglycaemia	166 (68.6)	17 (53.1)	40 (71.4)	12 (70.6)	30 (12.6)	7 (18.9)	5 (7.8)	2 (7.7)
Rash	112 (46.3)	21 (65.6)	41 (73.2)	3 (17.6)	7 (2.9)	4 (10.8)	15 (23.4)	1 (3.8)
Hypersensitivity and anaphylactic reaction	31 (12.8)	6 (18.8)	16 (28.6)	2 (11.8)	9 (3.8)	2 (5.4)	5 (7.8)	1 (3.8)
Pancreatitis	16 (6.6)	2 (6.3)	7 (12.5)	1 (5.9)	14 (5.9)	2 (5.4)	4 (6.3)	1 (3.8)
Osteonecrosis of jaw	11 (4.5)	1 (3.1)	5 (8.9)	0	3 (1.3)	0	2 (3.1)	0
Pneumonitis	4 (1.7)	1 (3.1)	1 (1.8)	0	4 (1.7)	0	0	0
Severe cutaneous reactions	1 (0.4)	0	4 (7.1)	0	0	0	0	0

Safety related to drug-drug interactions and other interactions

Within Study C2303, no new drug interaction studies had been conducted.

Discontinuation due to adverse events

In Study C2303, AEs leading to treatment discontinuation were more frequent with alpelisib plus fulvestrant than with placebo plus fulvestrant, including grade ≥3 events. The most common discontinuation events were consistent with the known safety profile of alpelisib, mainly rash, hyperglycaemia, pyrexia, diarrhoea, acute kidney injury and weight decrease. The pooled safety set showed a similar pattern.

Table 63 Adverse events leading to study drug discontinuation by preferred term (>1 participant in any group) and maximum grade (Safety Set)

	C2303 Alpelisib + Fluv N=92 All Grades n (%)	**Grade ≥ 3 n (%)**	**Placebo + Fluv N=94 All Grades n (%)**	**Grade ≥ 3 n (%)**	**C2301 Alpelisib + Fluv N=284 All Grades n (%)**	**Grade ≥ 3 n (%)**	**Placebo + Fluv N=287 All Grades n (%)**	**Grade ≥ 3 n (%)**	**Pool Alpelisib + Fluv N=376 All Grades n (%)**	**Grade ≥ 3 n (%)**	**Placebo + Fluv N=381 All Grades n (%)**	**Grade ≥ 3 n (%)**
Number of participants with at least one event	26 (28.3)	16 (17.4)	7 (7.4)	4 (4.3)	75 (26.4)	37 (13.0)	16 (5.6)	11 (3.8)	101 (26.9)	53 (14.1)	23 (6.0)	15 (3.9)
Hyperglycaemia	3 (3.3)	2 (2.2)	0	0	18 (6.3)	12 (4.2)	0	0	21 (5.6)	14 (3.7)	0	0

Rash	4 (4.3)	3 (3.3)	0	0	9 (3.2)	3 (1.1)	0	0	13 (3.5)	6 (1.6)	0	0
Diarrhoea	2 (2.2)	0	0	0	8 (2.8)	1 (0.4)	0	0	10 (2.7)	1 (0.3)	0	0
Fatigue	0	0	0	0	6 (2.1)	3 (1.1)	0	0	6 (1.6)	3 (0.8)	0	0
Nausea	1 (1.1)	0	0	0	5 (1.8)	1 (0.4)	0	0	6 (1.6)	1 (0.3)	0	0
Rash maculo-papular	3 (3.3)	3 (3.3)	0	0	3 (1.1)	1 (0.4)	0	0	6 (1.6)	4 (1.1)	0	0
Decreased appetite	0	0	0	0	4 (1.4)	0	0	0	4 (1.1)	0	0	0
Hypersensitivity	1 (1.1)	0	0	0	3 (1.1)	2 (0.7)	0	0	4 (1.1)	2 (0.5)	0	0
Lipase increased	1 (1.1)	1 (1.1)	0	0	3 (1.1)	1 (0.4)	5 (1.7)	4 (1.4)	4 (1.1)	2 (0.5)	5 (1.3)	4 (1.0)
Pneumonitis	1 (1.1)	1 (1.1)	0	0	3 (1.1)	1 (0.4)	0	0	4 (1.1)	2 (0.5)	0	0
Pyrexia	3 (3.3)	1 (1.1)	0	0	1 (0.4)	0	0	0	4 (1.1)	1 (0.3)	0	0
Stomatitis	0	0	0	0	4 (1.4)	1 (0.4)	1 (0.3)	0	4 (1.1)	1 (0.3)	1 (0.3)	0
Vomiting	0	0	0	0	4 (1.4)	0	0	0	4 (1.1)	0	0	0
Weight decreased	2 (2.2)	2 (2.2)	0	0	2 (0.7)	0	0	0	4 (1.1)	2 (0.5)	0	0
Acute kidney injury	2 (2.2)	1 (1.1)	0	0	1 (0.4)	1 (0.4)	0	0	3 (0.8)	2 (0.5)	0	0
Erythema	1 (1.1)	0	0	0	2 (0.7)	2 (0.7)	0	0	3 (0.8)	2 (0.5)	0	0
Dry mouth	0	0	0	0	2 (0.7)	1 (0.4)	0	0	2 (0.5)	1 (0.3)	0	0
Erythema multiforme	0	0	0	0	2 (0.7)	0	0	0	2 (0.5)	0	0	0
Hypokalaemia	1 (1.1)	1 (1.1)	0	0	1 (0.4)	1 (0.4)	0	0	2 (0.5)	2 (0.5)	0	0
Mucosal inflammation	0	0	0	0	2 (0.7)	1 (0.4)	0	0	2 (0.5)	1 (0.3)	0	0
Pneumonia	1 (1.1)	1 (1.1)	0	0	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)
Stevens-Johnson syndrome	1 (1.1)	1 (1.1)	0	0	1 (0.4)	1 (0.4)	0	0	2 (0.5)	2 (0.5)	0	0
Dyspnoea	0	0	1 (1.1)	0	1 (0.4)	0	1 (0.3)	0	1 (0.3)	0	2 (0.5)	0
Ejection fraction decreased	0	0	0	0	0	0	2 (0.7)	1 (0.3)	0	0	2 (0.5)	1 (0.3)

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported in the 'alpelisib' column.
A participant with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A participant with multiple adverse events is counted only once in the total row.
MedDRA version 27.1, CTCAE version 4.03

Dose interruption or changes due to adverse events

In Study C2303, adverse events leading to dose adjustments and/or treatment interruptions were more frequent with alpelisib plus fulvestrant than with placebo plus fulvestrant, including grade ≥3 events. The most common events were consistent with the known safety profile of alpelisib, mainly hyperglycaemia, rash, diarrhoea, decreased appetite, mucosal inflammation, nausea and pyrexia. The pooled safety set showed a similar pattern, with no additional adverse events leading to dose adjustments or interruptions in more than 5% of participants beyond those identified in Study C2303.

Table 64. Adverse events leading to dose adjustment and/or interruption by preferred term (>=5% participants in any group) and maximum grade (Safety Set)

	C2303				C2301				Pool			
	Alpelisib + Fluv N=92		Placebo + Fluv N=94		Alpelisib + Fluv N=284		Placebo + Fluv N=287		Alpelisib + Fluv N=376		Placebo + Fluv N=381	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Number of participants with at least one event	73 (79.3)	57 (62.0)	20 (21.3)	15 (16.0)	228 (80.3)	185 (65.1)	67 (23.3)	43 (15.0)	301 (80.1)	242 (64.4)	87 (22.8)	58 (15.2)
Hyperglycaemia	35 (38.0)	27 (29.3)	0	0	110 (38.7)	91 (32.0)	2 (0.7)	1 (0.3)	145 (38.6)	118 (31.4)	2 (0.5)	1 (0.3)
Diarrhoea	12 (13.0)	2 (2.2)	3 (3.2)	0	41 (14.4)	17 (6.0)	4 (1.4)	1 (0.3)	53 (14.1)	19 (5.1)	7 (1.8)	1 (0.3)
Rash	14 (15.2)	10 (10.9)	0	0	38 (13.4)	26 (9.2)	1 (0.3)	1 (0.3)	52 (13.8)	36 (9.6)	1 (0.3)	1 (0.3)
Rash maculo-papular	8 (8.7)	7 (7.6)	0	0	29 (10.2)	25 (8.8)	0	0	37 (9.8)	32 (8.5)	0	0
Stomatitis	4 (4.3)	3 (3.3)	0	0	18 (6.3)	6 (2.1)	0	0	22 (5.9)	9 (2.4)	0	0
Mucosal inflammation	7 (7.6)	1 (1.1)	0	0	14 (4.9)	4 (1.4)	0	0	21 (5.6)	5 (1.3)	0	0
Nausea	6 (6.5)	1 (1.1)	0	0	14 (4.9)	4 (1.4)	3 (1.0)	0	20 (5.3)	5 (1.3)	3 (0.8)	0
Decreased appetite	8 (8.7)	3 (3.3)	0	0	10 (3.5)	1 (0.4)	2 (0.7)	0	18 (4.8)	4 (1.1)	2 (0.5)	0
Pyrexia	5 (5.4)	0	3 (3.2)	0	11 (3.9)	2 (0.7)	2 (0.7)	1 (0.3)	16 (4.3)	2 (0.5)	5 (1.3)	1 (0.3)

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported in the 'alpelisib' column.
A participant with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A participant with multiple adverse events is counted only once in the total row.
MedDRA version 27.1, CTCAE version 4.03

Post marketing experience

The latest available Periodic Safety Update Report (PSUR), covering the period from May 2024 to May 2025, estimated a cumulative post-marketing exposure of approximately 14,533 patient-treatment-years. Based on the data reviewed in the PSUR, no new or changed safety signals were identified that would modify the established safety profile of alpelisib in its authorised indication.

2.5.1. Discussion on clinical safety

The safety profile of alpelisib is based on analyses from the double-blind periods of Studies C2303 and C2301 (SOLAR-1). Although some differences in baseline demographic characteristics were identified, given that Study C2303 was conducted exclusively in Europe and Canada whereas Study C2301 (SOLAR-1) included a broader geographic distribution, these demographic and disease characteristics are considered comparable. Therefore, the pooled safety data from both studies, as reflected in the SmPC, are deemed acceptable.

In the combined analysis of Studies C2303 and C2301 (SOLAR-1), a total of 376 participants were exposed to alpelisib plus fulvestrant, corresponding to 4577.6 participant-months of treatment exposure. This cumulative dataset provides a more robust characterisation of the safety profile of alpelisib in combination with fulvestrant.

At the data cut-off of Study C2303, the proportion of participants treated with alpelisib who discontinued the treatment study due to an adverse event was higher than the observed in Study C2301 (15.2% vs 4.9%, respectively); however, this difference did not translate into a meaningful change in the overall safety profile of alpelisib in this clinical setting. During the double-blind period of C2303 study, participants treated with alpelisib plus fulvestrant experienced a higher frequency of AEs compared with those receiving placebo plus fulvestrant, consistent with the findings from Study C2301. The number of participants reporting at least one SAE was also higher in the alpelisib arm than in the placebo arm; however, this proportion was lower in C2303 than in C2301 (22.8% vs 38.7% in the alpelisib arms, respectively). A similar pattern was observed for grade ≥3 SAEs, with lower frequencies reported in C2303 compared with C2301 (20.7% vs 32.7%, respectively). Nevertheless, the percentage of participants who reported a SAE in the placebo arm were similar between studies (18.8% in Study C2301 vs 19.1% in Study C2303). Moreover, a ≥5% difference in the reported SAEs between studies was observed only for hyperglycaemia (4.3% in Study C2303 vs 9.9% in Study C2301), which may be caused by the smaller sample size in Study C2303 and increased clinical experience over time in the recognition and management of adverse events, particularly hyperglycaemia. These facts, together with the double-blind study design support the conclusion that systematic under-reporting of SAEs in Study C2303 is unlikely.

The most common AEs of any grade reported in ≥15% of participants in the alpelisib plus fulvestrant arm of study C2303 were hyperglycaemia (72.8% vs 11.7%), diarrhoea (51.1% vs 11.7%), nausea (44.6% vs 13.8%), decreased appetite (30.4% vs 6.4%), rash (30.4% vs 1.1%), asthenia (27.2% vs 16.0%), mucosal inflammation (21.7% vs 0%), vomiting (18.5% vs 6.4%), stomatitis (16.3% vs 2.1%) and weight decreased (15.2% vs 1.1%). The most common grade ≥3 AEs in the alpelisib arm were hyperglycaemia (32.6%), rash (13.0%), maculopapular rash (7.6%) and weight decreased (5.4%). These findings are consistent with the previously established safety profile observed in Study C2301.

However, several AEs that were reported at ≥15% in the alpelisib arm of Study C2301 were not observed at comparable frequencies in Study C2303. These include alopecia (20.4% in C2301 vs 5.4% in C2303), pruritus (19.0% vs 7.6%), pyrexia (19.0% vs 14.1%), headache (19.0% vs 4.3%),

peripheral oedema (16.2% vs 7.6%), arthralgia (15.5% vs 8.7%), back pain (15.5% vs 3.3%) and dry skin (15.5% vs 3.3%). These frequency differences may be explained by different factors such as variations in sample size, data maturity and cumulative exposure, the increased physician familiarity with PI3K inhibitors over time, and the fact that in Study C2303 all participants were previously treated with CDK4/6 inhibitors, which share some common AEs with alpelisib, which may have influenced in AEs attribution and reporting. Furthermore, a lower incidence of these AEs was also observed in the placebo plus fulvestrant arm in Study C2303 compared with Study C2301, which, together with the double-blind design of the clinical trial, does not support systematic under-reporting.

The most common SAEs, reported in ≥2% of participants in the alpelisib arm, were hyperglycaemia (4.3%), acute kidney injury (2.2%), decreased appetite (2.2%), diarrhoea (2.2%) and rash (2.2%). In comparison with Study C2301, only hyperglycaemia occurred at a notably higher frequency in that trial than in Study C2303 (9.9% vs 4.3%). This difference may be related to improved recognition and management of alpelisib-associated hyperglycaemia over time, as the AE has become better characterised and is now more effectively managed with oral antidiabetic agents.

During the double-blind period of Study C2303, three on-treatment deaths occurred due to causes other than disease progression: hypovolemic shock, pneumonia, and pulmonary embolism. Among these, only the case of hypovolemic shock was considered by the investigator to be related to study treatment. An additional on-treatment death occurred in the crossover period due to hepatic encephalopathy. This event was deemed unrelated to treatment, as the participant had discontinued alpelisib due to disease progression, characterised by worsening of existing liver lesions, the appearance of new lesions, and ascites, which may plausibly explain the subsequent deterioration of liver function tests to Grade 3/4 prior to death. For the remaining three deaths reported in the crossover population (general physical deterioration, respiratory tract infection, and sepsis), these were not classified as on-treatment deaths.

The prespecified AESIs for Study C2303 included GI toxicity, hyperglycaemia, rash, hypersensitivity and anaphylactic reactions, pancreatitis, ONJ, pneumonitis and severe cutaneous reactions. GI toxicity was reported less frequently in Study C2303 than in Study C2301. Although GI toxicity forms part of the known safety profile of alpelisib, the potential contribution of metformin, commonly used to manage alpelisib-induced hyperglycaemia, cannot be excluded. Hyperglycaemia was very frequently observed, occurring in 72.8% of participants, with 4.3% requiring hospitalisation. In Study C2303 there were no serious complications reported such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic non-ketotic syndrome (HHNKS). In Study C2303 routine ketone screening was not mandatory. Nevertheless, it is acknowledged that DKA is a severe, acute, and life-threatening condition, which would be expected to be clinically recognised and appropriately managed if present by the investigators. In study C2303, as well as in study C2301, patients with type I diabetes or not controlled type II diabetes were excluded. For this reason, the recommendation stated in section 4.4 of the SmPC indicating that the safety of alpelisib in this population has not been established should be maintained. During Study C2303, 38% of participants received glucocorticoids, which may have further exacerbated the hyperglycaemia associated with alpelisib. However, during Study C2303 the concomitant use of glucocorticoids together with alpelisib did not contribute to the worsening of hyperglycaemia.

Rash, hypersensitivity and anaphylactic reactions, and severe cutaneous reactions were observed less frequently in Study C2303 compared with Study C2301. This reduction may be partly explained by the absence of Asian participants in C2303, as the race/region analysis conducted by the MAH showed that these AESIs were reported more frequently in Asian populations. In Study C2301, three cases of erythema multiforme were reported in Japanese participants, and for

the additional case of Stevens–Johnson syndrome, the participant's ethnic origin was not specified. Therefore, these AESIs appear to occur at higher rates among Asian participants, however neither study C2301 or C2303 included HLA genotyping or other genetic testing that may explain these differences observed in accordance to race. Other prespecified AESIs, such as elevations of pancreatic enzymes, pneumonitis, and ONJ, were also observed in Study C2303, and their frequency and severity were consistent with the already known safety profile of alpelisib.

Overall, the existing recommendations and precautions specified in 4.4 section of the SmPC are acceptable and should therefore be maintained for a safer use of alpelisib. No new ADRs have been identified, but some changes in frequencies have been reflected in the SmPC section 4.8.

Laboratory values in participants treated with alpelisib plus fulvestrant in Study C2303 were consistent with the previously known laboratory abnormalities described in Study C2301.

Drug discontinuations due to AEs are noteworthy, since 26.9% of participants in the pooled safety set discontinued due to an AE. Among these participants, only 14.1% were classified as grade 3 or higher, 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. antidiabetic medicinal products), that led to the discontinuation. Overall, this may indicate limited tolerability of alpelisib in combination with fulvestrant, which could be more pronounced in real-world clinical practice.

Safety in special populations did not include patients with renal or hepatic impairment, as previous clinical data had shown that neither mild nor moderate renal impairment nor mild, moderate or severe hepatic impairment resulted in clinically relevant alterations in the safety profile of alpelisib. However, caution is warranted in patients with severe renal impairment, as no clinical experience is available. No new safety concerns were identified in elderly participants, although there was

2.5.2. Conclusions on clinical safety

Based on the safety data from Study C2303 and its comparison with Study C2301, no new safety concerns associated with the newly targeted population were identified, and the overall safety profile of alpelisib remains consistent with its already established profile.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 10.1, dated 22 April 2026 is acceptable.

Safety concerns

Part II – Module SVIII (Summary of the safety concerns) remains unchanged. The overall safety profile of alpelisib remains consistent with its already established.

Table 65 Part II SVIII.1: 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

There are no additional pharmacovigilance activities that are planned or ongoing for alpesilib. In the RMP Part III.1, the existing targeted follow up questionnaire (FUQ) related to osteonecrosis of the jaw (ONJ) was removed following the PRAC request in procedure EMEA/H/C/006539/0000 to discontinue the existing targeted follow up questionnaire on ONJ for Piqray after 6 years in use in EU.

Risk minimisation measures

Table 66 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, 4.8, and 4.9 PL Sections 2, 3, 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist **Additional pharmacovigilance activities:** None
Pneumonitis	**Routine risk minimization measures:** SmPC Sections 4.4 and 4.8 PL Sections 2, 3, 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Severe cutaneous reactions	**Routine risk minimization measures:** SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2, 3, 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, 3, 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety with long-term use	**Routine risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Currently available data are limited and do not support the need for risk minimization. **Additional risk minimization measures:** None	None **Additional pharmacovigilance activities:** None

2.7. Update of the Product information

As a consequence of this new indication, section(s) 4.1, 4.2, 4.4, 4.8 and 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

This application does not include significant changes to the currently approved PL and therefore the results of the initial consultation with the target patient population are still considered valid and it is not considered necessary to perform any new user testing for this variation application.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The final indication is:

"*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 an endocrine-based regimen*** *(see section 5.1* ***and for biomarker based patient-selection see section 4.2****)*".

The aim of therapy in this setting is to reduce symptoms and prolong life while preserving quality of life.

3.1.1. Disease or condition

Globally, breast cancer is the most common cancer type among women and the second most common cancer type overall. An estimated 2.3 million new breast cancer cases and 670 000 breast cancer-related deaths occurred worldwide in 2022. In men, breast cancer is a rare condition constituting < 1% of all breast cancer diagnoses (Siegel et al, 2019). The predominant subset of breast cancer is HR-positive, HER2-negative that accounts for 65% to 75% of female breast cancer and 80% to 90% of male breast cancer. (Tarantino P et al, 2020, Deniziaut G et al, 2022). Approximately 40% of the tumors in patients with HR-positive, HER2-negative advanced breast cancer harbor a PIK3CA mutation (Fillbrunn M. et al, 2022). Patients with HR-positive, HER2-negative breast cancer whose tumor harbors a PIK3CA mutation and who progressed on endocrine-based regimens, including those with a CDK4/6 inhibitor, have a poor prognosis and limited treatment options (Fillbrunn M. et al[9], 2022, Yan M. et al[1], 2025).

3.1.2. Available therapies and unmet medical need

Endocrine therapy in combination with a CDK4/6 inhibitor is the regimen of choice for the first line treatment of HR-positive, HER2-negative advanced breast cancer patients (Cardoso et al, 5th ESO-ESMO, 2020).

In patients who relapse and whose tumours harbour a PIK3CA mutation, Piqray (alpelisib) is approved in the EU for patients who received first-line endocrine-therapy as monotherapy. Although alpelisib demonstrated efficacy in patients who had previously received endocrine therapy, at the time of initial MA, this efficacy could not be demonstrated in patients who had received endocrine therapy in combination with a CDK4/6 inhibitor due to the study population; which currently is the first-line treatment for those patients. Additional evidence was needed to support the use of alpelisib in these patients, since the most frequent scenario at this moment is that patients had received endocrine therapy in combination with a CDK4/6 inhibitor as first-line treatment.

After the EU marketing authorization of Piqray (alpelisib), new therapies targeting PIK3CA were approved: Itovebi (inavolisib), (PIK3CA inhibitor authorised in July 2025) and Truqap (capivasertib), (AKT inhibitor authorised in June 2024). Only capivasertib is indicated for a similar population as the sought indication for alpelisib: in combination with fulvestrant for the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen.

Although several treatment options exist for patients with HR-positive, HER2-negative, advanced breast cancer after disease progression on an endocrine-based regimen, this disease ultimately causes death within a limited number of years. Thus, there exists an unmet medical need for new treatment options, particularly treatments that can prolong time on endocrine-based regimens and treatments targeting tumours harbouring gene mutations associated to a poorer prognosis.

3.1.3. Main clinical studies

The basis for this submission was the study C2303, a phase III, randomized, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor. All patients had received a CDK4/6 inhibitor.

The study randomized 188 patients 1:1 to arm 1 (alpelisib 300 mg + fulvestrant 500 mg) or to arm 2 (placebo + fulvestrant 500 mg). Stratification factors were "presence of lung and/or liver metastases (yes/no)" and "setting at last prior CDK4/6 inhibitor therapy (adjuvant vs. metastatic)".

The primary endpoint was PFS by BIRC. Secondary endpoints were OS, ORR by BIRC, CBR by BIRC, DoR by BIRC, TTR by BIRC, PFS by BIRC by PIK3CA mutations status in ctDNA at baseline, TDD of ECOG performance status, change from baseline and TTD in QoL and symptom scale scores in EORTC QLQ-C30, and PFS2.

3.2. Favourable effects

PFS by BIRC was statistically significant at the IA [HR: 0.52 (95% CI: 0.37, 0.72; p-value < 0.0001; 66% events vs. 84% events] with an improvement of 4.6 months in the median PFS with alpelisib+fulvestrant compared with placebo+fulvestrant (7.4 months vs. 2.8 months, respectively). PFS by investigator was consistent. Sensitivity and subgroup analyses were also consistent.

At the **OS** FA an improvement was observed in the alpelisib+fulvestrant arm vs the placebo+fulvestrant [HR: 0.64 (95% CI: 0.41, 0.99) with 34/105 (32.4%) and 50/107 (46.7%) deaths respectively. mOS in the alpelisib+fulvestrant arm was 29.5 months (95% CI: 20.17, NE) vs. 23.8 months (95% CI: 17.28, 28.52) in the placebo+fulvestrant arm. Cross-over was allowed and 40.9% (43/105) of patients in the placebo+fulvestrant arm crossed over to the alpelisib+fulvestrant arm. The RPSFT analysis results for the FA, translated to an HR scale, yielded a cross-over adjusted HR point estimate of 0.52 (95% CI: 0.27, 0.98).

ORR was 23.4 % (95% CI: 15.3, 33.3) in the alpelisib+fulvestrant arm and 4.3% (95% CI: 1.2, 10.5) in the placebo+fulvestrant arm.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

In the pooled safety set, alpelisib plus fulvestrant was associated with a higher incidence of adverse events, grade ≥3 events, serious adverse events, treatment-related serious adverse events, and AEs leading to dose discontinuation, interruption or modification compared with placebo plus fulvestrant.

Based on the C2303 study, the main unfavourable effects were consistent with the known safety profile of alpelisib, including hyperglycaemia, gastrointestinal toxicity, rash, hypersensitivity/anaphylactic reactions, pancreatitis, osteonecrosis of the jaw, pneumonitis and severe cutaneous reactions. Of note, no new safety signals were identified. Deaths were mainly due to disease progression and were broadly comparable between treatment arms.

Overall tolerability continues to be a consideration, as a relevant proportion of AEs (26.9%) led to drug discontinuation, suggesting that tolerability may be limited in some patients and could be more pronounced under real-world conditions. Consequently, careful attention should be paid to hyperglycaemia-related issues and GI toxicity such as diarrhoea, both in the selection of patients and during treatment as reflected in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Patients with type I diabetes and those with poorly controlled type II diabetes were excluded from both pivotal studies; therefore, the safety profile in these populations remains unknown, particularly in relation to the risk of severe hyperglycaemic complications. Similarly, no participants with severe renal impairment (eGFR <30 mL/min/1.73 m²) were included, and safety in this subgroup has not been established. This is adequately reflected in the SmPC in 4.2 and 4.4.

3.6. Effects Table

Table 67 Effects Table for alpelisib in combination with fulvestrant for the treatment of patients with HR-positive, HER2- negative, advanced breast cancer with a PIK3CA mutation after disease progression following an endocrine-based regimen (data cut-off: 15-Oct-2024 and 26-May-2025)

Effect	Short description	Unit	Alpelisib + fulvestrant	Placebo + fulvestrant	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression-free survival (BIRC)	Median, months (95% CI)	7.4 (5.52, 9.10)	2.8 (1.94, 9.10)	HR: 0.52 (95% CI: 0.37, 0.72); p-value < 0.0001	CSR

(DCO: 15-oct-2024, primary analysis)						
OS (DCO: 26-May-2025; final analysis)	Overall survival	Median, months (95% CI)	29.5 (20.17, NE)	23.8 (17.28, 28.52)	HR: 0.64 (0.41, 0.99) Nominal p = 0.021	
ORR (DCO: 15-oct-2024, primary analysis)	Overall response rate (BIRC)	% (95% CI)	23.4 (15.3, 33.3)	4.3 (1.2, 10.5)	Patients with measurable disease at baseline were 85 in the alpelisib + fulvestrant arm vs. 90 in the placebo + fulvestrant arm	
Unfavourable Effects						
Grade 3-4	Incidence of grade 3 or 4 AEs	%	76.9	36.2		Clinical safety section of C2303 study and Summary of Clinical Safety.
SAEs	Incidence of serious AEs	%	34.8	18.9		
Discontinuations	Incidence of discontinuations due to AE	%	26.9	6.0		
Hyperglycaemia	Common AE	%	68.6	32.5		
GI Toxicity	AESI	%	75.5	32.5		
Rash	AESI	%	51.9	7.6		
Hypersensitivity and anaphylactic reactions	AESI	%	15.7	1.9		
ONJ	AESI	%	5.1	2.4		
Pneumonitis	AESI	%	1.6	0.5		
Severe cutaneous reactions	AESI	%	1.3	1.1		

Abbreviations:

Notes: *Cross-over was permitted: 40.9% (43/105) of patients crossed over from the placebo + fulvestrant arm to the alpelisib + fulvestrant arm.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Alpelisib in combination with fulvestrant has demonstrated a statistically significant and clinically relevant improvement in progression free survival by BIRC in HR-positive, HER2-negative, locally advanced or metastatic breast cancer patients with a PIK3CA mutation who progressed on endocrine therapy in combination with a CDK4/6i, when compared with fulvestrant alone. In this setting, a delay in disease progression is considered clinically relevant and can serve as the basis for granting an extension of the indication - provided no OS detriment is apparent. Besides, this improvement is supported by sensitivity and subgroup analyses, as well as by the higher antitumour activity shown with alpelisib+fulvestrant compared with fulvestrant alone. Furthermore, an improvement in OS was observed at the time of the final analysis, although this analysis was only descriptive.

From a safety point of view, alpelisib plus fulvestrant is considered more toxic than fulvestrant as monotherapy. Given the notable incidence of AEs leading to discontinuation, tolerability is concerning. Some uncertainties remain from a safety perspective including the exclusion of patients with type I diabetes and poorly controlled type II diabetes and the absence of data in patients with

severe renal impairment. Corresponding statements are included in the product information accordingly. However, no new safety signals have been identified in C2303 Study. Hyperglycaemia, gastrointestinal toxicity and rash remain as the main unfavourable effects of alpelisib. These can be considered generally manageable and reversible with dose adjustments and appropriate supportive care.

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 who progressed on endocrine therapy in combination with a CDK4/6i. Secondary endpoints also supported the primary analysis. No new safety concerns associated with the newly targeted population were identified, and the overall safety profile of alpelisib remains consistent with its already established profile.

3.7.3. Conclusions

The overall B/R of Piqray (alpelisib) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a)	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	II	I and IIIB

Extension of indication for 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 an endocrine-based regimen; based on the primary analysis (DCO 15-Oct-2024) from the Phase III Study CBYL719C2303 (C2303, EPIK-B5). This is a Phase III, randomized, double-blind, placebo-controlled study of alpelisib (BYL719) in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP has also been approved.

Amendments to the marketing authorisation

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

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.

In addition, 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.