Amsterdam, 21 May 2026
EMADOC-1829012207-22240
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vijoice

international non-proprietary name: Alpelisib

Procedure No. EMEA/H/C/006539/0000

Note

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

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List of abbreviations

AAFE	Absolute average fold error
ADME	Absorption, Distribution, Metabolism and Excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
AFE	Average fold error
AKT	Protein kinase B
AST	Aspartate aminotransferase
ATU	Temporary authorization for use
AUC	Area under the concentration-time curve
BChE	butyryl-choline esterase
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BIRC	Blinded independent review committee
BMI	Body mass index
BPI	Brief pain inventory
CDS	Core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance (Total body clearance of drug from the plasma [volume x time-1])
CLCR	Creatinine clearance [volume x time-1]
CLAPO	Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry with partial/generalized overgrowth
CLOVES	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration [mass x volume-1]
Cmin	Trough concentration
COA	Clinical outcome assessments
CSR	Clinical study report
CTAB	Cetyltrimethylammonium bromide
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse events
CTD	Common technical document
CYP3A4	Cytochrome P450 family 3A4
DDI	Drug-drug interaction
DMPK	Drug Metabolism & Pharmacokinetics
DOR	Duration of response
DSC	Differential Scanning Calorimetry
EC	European Commission
eCRF	Electronic case report form
E-R	Exposure -response
EU	European Union
FAS	Full analysis set
FASP	FAS for the prospective period

FCT	Film-coated tablet
FDA	Food and Drug Administration
FMI	Final Marketing Image
GC	Gas Chromatography
GCP	Good clinical practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HA	Health authority
HFHC	High fat high calorie
HPLC	High performance liquid chromatography
HR-MS	High resolution mass spectrometry
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
IRT	Interactive Response Technology
KF	Karl Fischer titration
KTS	Klippel-Trenaunay syndrome
LDPE	Low density polyethylene
LFLC	Low fat low calorie
LON	lipomatosis of nerve
MAA	Marketing authorization application
MAP	Managed access program
MCAP	Megalencephaly-capillary malformation polymicrogyria
MDD	Maximum daily dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NMR	Nuclear Magnetic Resonance
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamics
PGIS	Patient global impression of symptom severity
Ph. Eur.	European Pharmacopoeia
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphatidylinositol-3-kinase catalytic alpha polypeptide (gene which encodes the p110-α catalytic subunit of PI3K)
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PK/PD	Pharmacokinetics-Pharmacodynamics
popPK	Population PK
PRO	Patient-reported outcome
PROMIS	Patient-reported outcome measurement information system
PROS	PIK3CA-related overgrowth spectrum
PT	Preferred term
QTPP	Quality target product profile
RH	Relative Humidity
RMP	Risk management plan
SAP	Statistical analysis plan
SAE	Serious adverse event

SCARs	Severe cutaneous adverse reactions
SD	Standard deviation
SJS	Stevens-Johnson-Syndrome
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedures
SP	eCRS flag for safety profiling plan (i.e. the core safety flag)
Tmax	Time to reach maximal drug concentration
t1/2	Terminal elimination half-life
ULN	Upper limit of normal
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1.1. Protocol assistance

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality/ non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
27 February 2020	Clinical	EMEA/H/SA/2907/4/2019/II	The Scientific advice pertained to the following clinical aspects: • Agreement of the unmet medical need in PROS. • Acceptability of a retrospective chart review of patients with PROS treated with alpelisib in a compassionate use program to assess clinical outcomes to support a CMA. • Acceptability of a randomised Phase II, double-blind, placebo-controlled study, in particular regarding the design, patient population, statistical analysis plan, sample size and proposed doses to assess the efficacy, safety and pharmacokinetics of alpelisib in pediatric and adult patients with PROS and the suitability of this study for conversion from conditional to regular MA.
14 October 2021	Clinical and quality	EMA/SA/0000067212	The Protocol assistance pertained to the following quality and clinical aspects: Quality: •Drug product stability and shelf-life to be included in

			MAA. •Strength biowaiver to be included in MAA. Clinical: •If the previous concerns raised by the CHMP in relation to the retrospective chart review study EPIK-P1, and a conditional marketing authorisation application (CMA) based on it, have been adequately addressed. In particular related to: non-standard data collection involved in EPIK- P1, the proposed indication not being reflective of the EPIK-P1 population, lack of comparative assessment with patients not treated with alpelisib, absence of PK data to justify the pediatric dose, lack of paediatric safety data, small size of safety database in PROS, recruitment in/drop -out of patients from the prospective Phase II study (EPIK-P2) study should conditional marketing authorization be granted. •Submission of an MAA for CMA based on data from EPIK-P1. •MAA submission based on the EPIK-P2 primary analyses at Week 24 should an MAA submission based on EPIK-P1 not be accepted. Proposal for revised EPIK-P2 study design based on data from EPIK-P1.
25 May 2023	Non-clinical and clinical	EMA/SA/0000136213	The Protocol assistance pertained to the following non-clinical and clinical aspects: • Environmental risk assessment for the new pharmaceutical form • Bioequivalence of alpelisib 50 mg granule and 50 mg film-coated tablet formulation and the food effect of alpelisib

			granule formulation; agreement that no additional clinical data are required to support a line extension for the 50 mg granule formulation; need for a further consultation with target patient groups.

1.2. Eligibility to the centralised procedure

The applicant Novartis Europharm Limited submitted on 5 May 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Vijoice (alpelisib), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 March 2024.

The applicant applied for the following indication:

Vijoice is indicated 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.

1.3. Legal basis and dossier content

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies.

1.4. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0412/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0412/2022 had not yet been completed as some measures had been deferred.

1.5. Information on orphan market exclusivity

Vijoice was designated as an orphan medicinal product EU/3/21/2420 on 26/03/2021 in the following condition: Treatment of PIK3CA related overgrowth spectrum.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Vijoice as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: Vijoice | European Medicines Agency (EMA).

1.5.1. Similarity with authorised orphan medicinal products

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

1.6. Applicant's request(s) for consideration

1.6.1. Conditional marketing authorisation (CMA)

The applicant requested consideration of its application for a conditional marketing authorisation (CMA) in accordance with Article 14-a of Regulation (EC) No 726/2004 (see section 9.6.3.3).

1.6.2. New active substance status

Not applicable.

1.7. Patient experience data

Table 2: Patient experience data relevant to the application

Patient experience data submitted with this application			*Section where discussed (if applicable)*
☐	Patient experience data submitted by the applicant:		
	☐	Clinical outcome assessments (COAs) such as	
		Patient-reported outcomes (PRO)	
		Other	
	☐	Patient preference studies	
	☐	Observational studies/RWD designed to capture patient experience data	
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)	
	☐	Other (please specify)	
☒	Other patient experience data not submitted by the applicant but considered in this evaluation:		
	☐	Input informed from participation in meetings or public hearings with patient stakeholders	
	☒	CHMP early dialogue with patient organisations	
	☐	Third party interventions from patients and patient groups	
	☐	Other (e.g.	

Patient experience data submitted with this application			Section where discussed (if applicable)
		medical literature, summaries/analysis from patient engagement activities - please specify)	

1.8. Steps taken for the assessment of the product

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

Rapporteur:	Nicolas Beix
Co-rapporteur:	Carolina Prieto Fernandez

The application was received by the EMA on	5 May 2025
The procedure started on	22 May 2025
The CHMP rapporteur's first assessment report was received on	11 August 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	25 August 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	18 September 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	4 February 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint updated assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	20 February 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 February 2026
An expert group was convened to address questions raised by the CHMP on The CHMP considered the views of the expert group as presented in the minutes of this meeting.	13 March 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	23 March 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	8 April 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint updated assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	17 April 2026
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	23 April 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing	21 May 2026

authorisation to Vijoice on	

1.9. CHMP outcome

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

The CHMP reviewed the available paediatric data of studies subject to the agreed paediatric investigation plan (PIP) P/0412/2022 and the results of these studies are reflected in the summary of product characteristics (SmPC) and, as appropriate, the package leaflet.

Relevant paediatric statement in Section 5.1 of the SmPC if the EMA has deferred a paediatric development have also been included.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.9.2.1. Similarity with authorised orphan medicinal products

Not applicable.

1.9.3. Opinion

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

Vijoice is indicated 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 CHMP, therefore, recommends the granting of the conditional marketing authorisation subject to the conditions described in the following sections.

1.9.3.1. Divergent position

Divergent position to the majority recommendation on benefit/risk – full CHMP opinion is appended to this report.

1.9.4. Conditions or restrictions regarding supply and use

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

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder shall submit periodic safety update reports every 6 months.

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

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

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

1.9.6.1. Risk management plan (RMP)

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

An updated RMP should be submitted:

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

1.9.7. Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the applicant shall complete, within the stated timeframe, the following measures:

Table 3: Specific obligations

Description	*Due date*
In order to further confirm the efficacy, safety and pharmacokinetics of alpelisib in the treatment of adult and paediatric patients with PIK3CA-related overgrowth spectrum (PROS), the MAH should submit the final results of the phase II single arm study CBYL719F12202 (EPIK-P4).	31 December 2032

1.9.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.9.9. Proposed list of recommendations

Table 4: Proposed list of recommendations

Description of recommendation(s)
Submission of the results of the 26-weeks carcinogenicity study in transgenic mice: Q4 2027

2. Introduction

2.1. Therapeutic context

PIK3CA-related overgrowth spectrum (PROS) is an umbrella term encompassing a diverse group of rare, phenotypically variable, disorders stemming from sporadic somatic gain-of-function mutations in the PIK3CA gene, including but not limited to: fibroadipose hyperplasia or overgrowth (FAO), hemihyperplasia multiple lipomatosis (HHML), congenital lipomatosis with overgrowth, vascular malformations, epidermal nevi, and skeletal/scoliosis/spinal abnormalities (CLOVES) syndrome, macrodactyly, fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis, megalencephaly-capillary malformation polymicrogyria (MCAP), dysplastic megalencephaly, capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry with partial/generalized overgrowth (CLAPO), lipomatosis of nerve (LON), and Klippel-Trenaunay syndrome (KTS) (Keppler-Noreuil et al 2015, Hughes et al 2020).

The prevalence of PROS in the European Union (EU) is predicted to be < 5 per 10,000, and as such, alpelisib was granted an orphan designation for the treatment of PROS on March 2021.

The clinical characteristics of PROS can be diverse and depend on the timing of the mutation during embryogenesis and the organs affected. PROS is characterized by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. Segmental overgrowth is often congenital in onset, but it is usually noted by 1 year of age with progressive overgrowth of tissues persisting in some cases into adulthood (Keppler-Noreuil et al 2016). PROS syndromes are clinically recognizable conditions and are associated with cutaneous, vascular, musculoskeletal, and/or cerebral abnormalities, as well as focal or segmental overgrowth of the body. PROS may be conceived as a highly anatomically variable mixture of overgrown tissues, with vasculature (capillaries, veins and lymphatics) and adipose tissues often most dramatically affected macroscopically. Many other tissues and organs, including bone, brain, peripheral nerves, liver, and skeletal and cardiac muscles can also be affected.

The clinical impact of PROS depends on the anatomical site and extent of overgrowth and may include functional impairment (e.g. of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infection, impaired neurological development, seizures, thromboembolism, pulmonary hypertension, haemorrhage, as well as other manifestations that can be a consequence of overgrowth. The severity of PROS is highly variable, ranging from localized overgrowth to severe, extensive, and life-threatening overgrowth affecting major vessels and/or critical organs. There are currently no established severity criteria available for PROS (Keppler-Noreuil et al 2016, Madsen et al

2018, Broder et al 2023). PROS is a progressive disease by nature; no disease improvement is expected without active therapy. Patient advocates report a multitude of direct impacts including deformity, pain, neurological deficits, complications such as infections and thrombosis, and psychological issues. The conditions impact patients and families at all stages of development as they try to cope with complex health needs and everyday activities such as going to school (Rodríguez-Laguna et al 2022).

Current treatment options and unmet need

There is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for this disease in the EU. Current treatment relies on supportive care and is comprised of surgical debulking, amputations, orthopaedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure). Patients often experience recurrence following surgery, and repeated surgeries are frequently required.

Given the genetic background of PROS, sirolimus, an mTOR inhibitor, has been studied and is sometimes used off label in patients with PROS, however, its use has been associated with limited efficacy and frequent adverse events (AEs) (Parker et al 2019). Lastly, supportive care is routinely provided to patients with PROS and may include pain and symptoms management, nutritional support, and psychological support (Venot et al 2018, Engel-Nitz et al 2021, Canaud et al 2023, Douzgou et al 2022). Of note, when clinicians initiate treatment in patients with PROS, their objective is to achieve a reduction in PROS lesions' volume as this is expected to translate into improvements in disease-related symptoms and provide clinical benefit to patients.

Therefore, patients with severe or life-threatening manifestations of PROS have a significant unmet medical need for new and effective therapeutic approaches, including pharmacological treatments that target the underlying cause of the disease (i.e. PIK3CA mutation) which is currently unavailable.

2.2. Aspects of development

Alpelisib was first used in France for the treatment of 2 patients (1 adult and 1 paediatric) with severe or life-threatening PROS (more specifically, CLOVES) as part of a compassionate use program called in France "nominative Temporary Authorization for Use (ATU)". Supported by encouraging clinical improvements in these patients, the physicians were authorized to administer alpelisib to 17 additional patients with PROS who had severe or life-threatening complications and/or were scheduled for debulking surgery. In total, alpelisib was used to treat 19 patients (4 adults and 15 paediatrics, with the youngest being 4 years old) with PROS at a single centre; results were published (Venot et al 2018).

Based on the published results, alpelisib was administered to an increasing number of patients with PROS via compassionate use programs in several countries worldwide (i.e. under ATU CBYL719XFR01I and CBYL719X2001I in France and under Treatment Plan CBYL719F12001M [Managed Access Program; MAP] outside France). The compassionate use program recommended that an alpelisib 50 mg dose, taken with food, be used in paediatric patients (2 to 17 years), while an alpelisib 250 mg dose, taken with food, be used in adult patients (≥ 18 years). To date, over 850 patients with PROS have received treatment with alpelisib under the compassionate use programs.

Considering that a number of patients were being treated globally under the compassionate use programs, the applicant initiated a development program for alpelisib in PROS consisting mainly of the three studies: Study CBYL719F12002 (EPIK-P1) and Study CBYL719F12401 (EPIK-P3), followed by CBYL719F2201 (EPIK-P2).

EPIK-P1 was a site-based, retrospective, non-interventional medical chart review of patients 2 years of age and older with severe or life-threatening PROS who received alpelisib as part of a compassionate use program (i.e. patients were treated under the ATU in France or the MAP outside France). This completed study, with a cut-off date of 09-Mar-2020, allowed for the retrospective collection of data from the medical records of patients treated through compassionate use programs.

At the time of completion of EPIK-P1 study, most patients continued to receive treatment with alpelisib. To allow for the collection of longer-term data in these patients, EPIK-P3 study protocol was released.

EPIK-P3 was designed to evaluate the long-term safety and efficacy of alpelisib treatment in paediatric and adult patients with severe or life-threatening PROS who participated in EPIK-P1 and continued to receive treatment with alpelisib after the EPIK-P1 cut-off date within the global compassionate use program.

EPIK-P2 is an ongoing prospective Phase II, multi-centre study with an upfront 16-week, randomized, double-blind, placebo-controlled period, followed by two extension periods to assess the efficacy, safety and PK of alpelisib in paediatric and adult patients with PROS irrespective of the disease severity. EPIK-P2 will have an overall follow-up of approximately 5 years to collect long-term efficacy and safety data in patients with PROS.

2.3. Description of the product

Alpelisib (BYL719), administered orally, is an effective oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. Class I PI3K lipid kinases are key components of the PI3K/AKT/mTOR (mammalian target of rapamycin) signalling pathway. Gain-of-function mutations in the gene encoding the catalytic alpha-subunit of PI3K (PIK3CA) lead to the activation of PI3Kalpha manifested by increased lipid kinase activity, growth-factor independent activation of AKT-signalling, cellular transformation, and the generation of tumours in the in vitro and in vivo models. This is the underlying mechanism for several cancers and the different lesions in the PROS disease.

Alpelisib has demonstrated antitumor activity in a variety of cancer cell lines, particularly those harbouring PIK3CA mutations and in xenograft models with mutated or amplified PIK3CA gene (Keegan et al 2018). Alpelisib (Piqray) in combination with fulvestrant was approved for the treatment of post-menopausal women, and men, with HR-positive, HER2- negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy.

Considering the shared underlying genetic background with hyperactivation of the PI3K/AKT/mTOR pathway, alpelisib was studied in a mouse model of PROS/CLOVES, which partially recapitulates human disease (De Santis et al 2017, Canaud et al 2021). In this model, alpelisib inhibition of PI3K pathway resulted in the prevention of onset of PROS lesions and improvement of established tissue abnormalities as detected by magnetic resonance imaging (MRI) such as scoliosis, muscle hypertrophy, and vessel malformation. Furthermore, alpelisib withdrawal led to the recurrence of tumours and the development of asymmetric extremity hypertrophy. These data from mice suggested that continuous administration of alpelisib may control PROS lesions and relieve PROS symptoms by inhibiting the hyperactive cell-signalling pathway resulting from PI3KCA gene mutation (Venot et al 2018).

The proposed indication by the Applicant is as follows: "*Vijoice is indicated 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*".

For the treatment of severe or life-threatening manifestations of PROS, the recommended dose in adult patients is 250 mg q.d. with food and the recommended starting dose for paediatric patients aged 2 to

17 years is 50 mg q.d. with food, with up-titration to a maximum dose of 125 mg q.d. with food as needed for response optimization in patients aged 6 to 17 years after at least 24 weeks of treatment at 50 mg. Paediatric patients are recommended to gradually increase to the adult dose when 18 years of age is attained. The 50 mg dose can be administered using FCT or granules. All dose levels may be administered using gastric or nasogastric feeding tubes with granules (50 mg dose) or crushed FCT (doses higher than 50 mg).

Exposure-response (ER) and Pharmacokinetics-Pharmacodynamics (PK/PD) modelling provide evidence of a positive relationship between exposure and both PD and clinical response, indicating the effectiveness of PROS treatment with alpelisib and supporting dose escalation as needed for response optimization in patients aged 6 years and older.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

The pivotal toxicology and safety pharmacology studies were conducted in accordance with GLP regulations and ICH guidelines, i.e. supported by an adequate quality assurance system including in study audits. No reasons to trigger a GLP inspection were observed.

No specific GLP comment is raised on the newly submitted 2-year rat carcinogenicity study. This study could be considered as GLP compliant.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

The finished product is presented as film-coated tablets for oral administration containing 50 mg, 125 mg or 200 mg of alpelisib and also as granules in a sachet containing 50 mg of alpelisib.

For the film coated tablets the other ingredients are:

Tablet core - cellulose microcrystalline (E460), mannitol (E421), sodium starch glycolate, hypromellose (E464) and magnesium stearate (E470b).

Film coating - hypromellose (E464), iron oxide yellow (E172), iron oxide red (E172) applicable only to 50 mg and 200 mg strengths, titanium dioxide (E171), macrogol (E1521) and talc (E553b).

For the granules the other ingredients are:

Cellulose microcrystalline (E460), mannitol (E421), sodium starch glycolate, hypromellose (E464), and magnesium stearate (E470b).

The product is available in a polyvinylchloride/polychlorotrifluoroethylene/aluminium blister for the tablets and a polyethylene terephthalate/aluminium/polyethylene foil sachet for the granules as described in section 6.5 of the SmPC.

3.2. Active substance

3.2.1. General information

The chemical name of alpelisib is (2S)-N1-{4-Methyl-5-[2-(1,1,1-trifluoro-2- Methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl}pyrrolidine-1,2-dicarboxamide corresponding to the molecular formula $C_{19}H_{22}F_3N_5O_2S$. It has a relative molecular mass of 441.47 g/mol and the following structure:

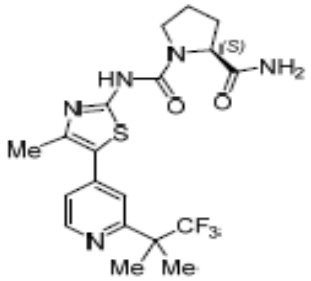


Figure 1: active substance structure

The chemical structure of alpelisib was elucidated by a combination of HR-MS, IR, UV, ^{1}H-NMR & ^{13}C-NMR. The solid state properties of the active substance were measured by DSC & XRPD

The active substance is a white to almost white powder, it has poor solubility in aqueous conditions across the physiological pH range and it is slightly hygroscopic.

Alpelisib exhibits stereoisomerism due to the presence of one chiral centre. This originates in the one of the starting materials and potential chiral impurities are controlled in the specification of the starting material and enantiomeric purity is controlled in the specification of the active substance.

Polymorphism has been observed for alpelisib, however only one crystalline anhydrous form (form A) has been identified. The other forms identified are solvates obtained through specific equilibration with organic solvents. The polymorphic form is controlled in the specification of the active substance; it has been shown that the active substance manufacturing process consistently produces this form and that it is stable during storage.

3.2.2. Manufacture, characterisation, and process controls

Alpelisib is synthesised in five main steps using well defined starting materials with acceptable specifications. The active substance is manufactured at one proposed manufacturing site, and satisfactory information concerning GMP standards has been provided.

The active substance is synthesised through a convergent synthesis process and the information concerning the active substance is acceptable. It is also of note that the process is the same as for the authorised medicinal product Piqray which is approved through the centralised procedure.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

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

The active substance is packaged in double LDPE bags stored in a metal drum. The primary packaging material complies with Commission Regulation (EU) 10/2011, as amended.

3.2.3. Specification

The active substance specification includes tests for appearance, particle size distribution (laser diffraction), identity (IR, XRPD), assay (HPLC), impurities (HPLC), enantiomer (chiral HPLC), residual solvents (GC), water content (KF), sulfated ash (Ph. Eur.), and microbial enumeration (Ph. Eur.). The specification presented relates to the granule formulation, the same specifications/parameters are applied to the tablet formulation with the exception of a differing value for the particle size distribution.

The active substance specifications have been set considering the physico-chemical characteristics and intended use of the substance, the intended finished product, the maximum daily dose of alpelisib, the toxicological qualification, and relevant guidelines. The proposed specifications are considered acceptable.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The qualified specified impurities are also metabolites. The limit for benzene is according to ICH Q3C.

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

Batch analysis data from 15 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

3.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) were provided. In addition, supportive data from six pilot scale batches manufactured from another manufacturing site were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results of stress conditions which involved exposure to increased temperature and humidity along with results of exposure to aqueous, acidic, basic and oxidative conditions were also provided on one batch.

The following parameters were tested*:* appearance, identity, impurities, enantiomer, water content, assay and microbial enumeration. The analytical methods used were the same as for release and were stability indicating.

At long term and accelerated conditions all tested parameters were within the specifications, a small increase in one related substance was noted at one timepoint in one batch but this remained within the relevant specification. The results of photostability showed an increase in impurities and a decrease in assay values which led to out of specification results, the active substance is therefore considered photosensitive. In the stress testing conditions it was observed that the active substance is sensitive to hydrolytic, acidic, basic and oxidative stress conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the applicant's selected retest period of 48 months below 30 °C while protected from light in the proposed container. This proposed temperature storage condition is more restrictive than the available data suggest is required, however, the storage of the active substance prior to finished product manufacture does not impact the patient.

3.3. Finished medicinal product: Film-coated tablets

3.3.1. Description of the product and pharmaceutical development

The film-coated tablet formulations are proposed in three strengths with the following appearance:

Vijoice 50 mg film-coated tablets

Light yellow, round, curved film-coated tablet with bevelled edges, debossed with "C7" on one side and "NVR" on the other side. Approximate diameter: 7 mm.

Vijoice 125 mg film-coated tablets

Dark yellow, ovaloid, curved film-coated tablet with bevelled edges, debossed with "Y7" on one side and "NVR" on the other side. Approximate size: 13 mm (length) x 6 mm (width).

Vijoice 200 mg film-coated tablets

Pale yellow, ovaloid, curved film-coated tablet with bevelled edges, debossed with "CL7" on one side and "NVR" on the other side. Approximate size: 16 mm (length) x 7 mm (width).

The aim of development was to formulate immediate release film-coated tablets suitable for the intended patient population. The applicant has experience gained from the previous authorisation of Piqray film-coated tablets which contain the same active substance. The development therefore leveraged this knowledge, for example, the same formulation is used with the exception of the film-coating agent. The tablet cores are dose proportional. The intended indication includes adults and paediatric patients who are capable of swallowing tablets. For paediatric patients who cannot swallow the tablets satisfactory information has been provided on the preparation of a suspension in water and also for the potential administration through enteral feeding tubes. These aspects are reflected in the product information. The applicant has also developed a granule formulation intended for those who cannot swallow whole tablets and this formulation is discussed separately in this report. The following Quality Target Product Profile (QTPP) was defined for the tablet formulations.

Table 1: Quality Target Product Profile: Film-coated tablets

Quality attributes	Product profile
Indication	Treatment of PROS (PIK3CA Related Overgrowth Spectrum)
Mechanism	Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα

Quality attributes	Product profile
Route of administration	Oral
Clinical requirements/ dosing scheme	Up to 250 mg/day
Marketing requirement	The target population consists of pediatrics and adults
Dosage form / strengths/ color, shape and size	Film-coated tablet; 50 mg, 125 mg, and 200 mg 50 mg: Light yellow, unscored, round and curved film-coated tablet with beveled edges. Diameter: approx. 7.2 mm 125 mg: Dark yellow, unscored, ovaloid and curved film-coated tablet with beveled edges. Length: approx. 13.2 mm, Width: approx. 5.7 mm 200 mg: Pale yellow, unscored, ovaloid and curved film-coated tablet with beveled edges. Length: approx. 16.2 mm, Width: approx. 6.5 mm
Debossing strategy	50 mg: Debossed with "C7" on one side and "NVR" on the other side 125 mg: Debossed with "Y7" on one side and "NVR" on the other side 200 mg: Debossed with "CL7" on one side and "NVR" on the other side
Packaging strategy	Alpelisib film-coated tablets are packaged in PVC/PCTFE/Alu blisters
Storage condition	Do not store above 30°C, protect from moisture
Labeling instructions	In accordance with local requirements
Drug release profile	Immediate release Alpelisib storage requires protection from light.

The active substance is poorly soluble and the solid state characteristics which could impact the performance of the finished product are controlled in the specification of the active substance with a control for polymorphic form and the particle size distribution included.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards with the exception of the in-house coating materials. For the in-house coating materials suitable specifications have been provided. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients are considered acceptable in line with the intended paediatric and adult use of the formulations.

The formulation used during clinical studies is the same as that intended for marketing.

The manufacturing process was developed in consideration of the knowledge from the similar formulation for Piqray. The same type of conventional wet granulation process is used with the same common blend. The active substance is a high proportion of the formulation and the selected particle size distribution aids manufacturability and prevents sticking/pitting and allows improved compressibility. The suitability of the proposed process was determined during development including the parameters related to the film-coating process.

The dissolution method uses 900 ml of pH 4.5 media with 0.6% CTAB and the paddle apparatus at 75 rpm. The conditions chosen for the dissolution method has been suitably justified and the discriminatory power of the dissolution method has been demonstrated.

The primary packaging is a polyvinylchloride/polychlorotrifluoroethylene/aluminium blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of four main steps: The process is considered to be a standard manufacturing process.

The manufacturing process is adequately described; critical steps were clearly stated with appropriate in-process controls to be applied during the process.

with appropriate in-process controls to be applied during the process. There are no isolated intermediates in the manufacturing process.

Major steps of the manufacturing process have been validated by the production of three consecutive commercial scale validation batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Validation of the bulk product hold time is provided. A shipping evaluation study was also performed.

3.3.3. Product specification

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

The specifications are acceptable and describe relevant acceptance criteria to ensure consistent quality. The justification of the specifications is based on the collective data obtained for clinical, registration stability, pre-validation, validation and commercial stability batches of Piqray tablets. In addition, data obtained on pre-validation, validation/commercial batches of alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets with the formulations as mentioned above were also considered.

Limits were set taking into account the maximum daily dose (MDD) not exceeding 400 mg of alpelisib drug substance for Piqray as well as the experience gained during development. For the proposed PROS indication a maximum daily dose of 250 mg in adults is established for the 50 mg, 125 mg, and 200 mg film-coated tablets and it is therefore accounted for.

Two degradation products are specified and both are considered suitably qualified as metabolites of the active substance.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results were provided for three commercial scale batches of each strength along with considerable batch analysis data from clinical and pre-validation batches. The batch analysis results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.3.4. Stability of the product

Stability data from three commercial scale batches of each strength of the finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH & 30 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are indentical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Supportive stability was provided for the similar Piqray formulation which included 36 months of long term data.

Samples were tested for appearance, water content (KF), dissolution (UV), degradation products (HPLC), assay (HPLC) and microbial enumeration (Ph. Eur.). At long term and accelerated conditions no out of specification results or significant trends were noted.

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

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. Finished medicinal product: Granules in sachet

3.4.1. Description of the product and pharmaceutical development

The granule formulation is proposed in one strength which is 50 mg, and the granules are white to almost white in colour.

The aim of development of the granules was to create an alternative formulation for those who may have difficulty in swallowing the tablet formulations. Satisfactory information has been provided regarding mixing the granules with certain foods such as yogurt or certain liquids such as water or apple juice. Similarly, information has been provided substantiating the potential to use the granules with enteral feeding tubes. These aspects are suitably described in the product information. The following QTPP was defined for the granule formulation.

Table 2: Quality Target Product Profile: Granules

Quality attributes	Product profile
Indication	PROS (PIK3CA Related Overgrowth Spectrum)
Route of administration	Oral
Dosage form	Granules
Delivery system	Immediate release
Dosage strength	50 mg
Container closure system	Sachets

Quality attributes	Product profile
Pharmacokinetics (Bioavailability)	Comparable PK profile between tablet and granules dosage form based on the BE study (CBYL719F12101)
Stability	Minimum shelf life of 24 months
Drug product quality criteria	Details of the drug product quality criteria for the intended commercial product are provided in section [3.2.P.5.6]

The solid state characteristics which could impact the performance of the finished product are controlled in the specification of the active substance with a control for polymorphic form and the particle size distribution included.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients are considered acceptable in line with the intended paediatric and adult use of the formulations.

The formulation and manufacturing process were selected and developed using knowledge gained from the development of the tablet formulations. The same excipients are used as in the cores of the film-coated tablets with differing grades and amounts of some excipients present to generate a suitable granule formulation. A wet granulation based process was also selected for the manufacture of the granule formulation. The suitability of the proposed process was determined during development including the parameters related to granulation and sachet filling. The information gained during development was used to inform the proposed control strategy for the commercial process.

The proposed 50 mg granule formulation was compared to the proposed 50 mg film-coated tablet formulation through a bioequivalence study. The information concerning bioequivalence was shown to be acceptable, for further information concerning this please refer to the clinical sections of this report.

The dissolution method for control of the granules uses the same conditions as for the film-coated tablets 900 ml of pH 4.5 media with 0.6% CTAB and the paddle apparatus at 75 rpm. The discriminatory power of the dissolution method has also been demonstrated for the granule formulation.

The primary packaging is a polyethylene terephthalate/aluminium/polyethylene foil sachet. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.4.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of four main steps: The process is considered to be a standard manufacturing process.

The manufacturing process is adequately described; critical steps were clearly stated with appropriate in-process controls to be applied during the process.

Major steps of the manufacturing process have been validated by the production of three consecutive commercial scale validation batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

3.4.3. Product specification

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

The specifications are acceptable and describe relevant acceptance criteria to ensure consistent quality. Similar to the proposed tablets, the MDD of alpelisib was considered as a worst case scenario in setting specifications for the granules.

As per the tablet formulation two degradation products are specified and both are considered suitably qualified as metabolites of the active substance.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

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

Batch analysis results have been provided for nine commercial scale batches which included the batch used for the bioequivalence study. The batch analysis results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.4.4. Stability of the product

Stability data from six commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH & 30 °C/ 75% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content (KF), dissolution (UV), degradation products (HPLC), assay (HPLC) and microbial enumeration (Ph. Eur.). The analytical procedures used are stability indicating. At long term and accelerated conditions no out of specification results or significant trends were noted. An increase in one of the degradation products was noted after 36 months of storage at 30 °C/ 75% RH but the results remain well within specification.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The granules are photosensitive and the intended packaging provides suitable protection from light during storage.

Based on available stability data, the proposed shelf-life of 36 months and instruction to store in the original sachet in order to protect from light as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

3.4.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.6. Conclusions on the chemical, and pharmaceutical aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.7. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The present application by Novartis concerns a conditional marketing authorisation (CMA) application through the centralised procedure. As alpelisib (PIQRAY) is already authorised for the treatment of advanced cancers, the toxicology program had been designed in accordance with ICH S9 guideline. PROS syndrome is outside the scope of ICH S9 guideline. Toxicological profile was investigated in rat and dogs up to 13-week treatment duration, chronic studies were not conducted but the available clinical experience is considering sufficient to not request additional animal safety studies.

To evaluate the potential effect of alpelisib on reproductive potential and embryofetal development, a GLP fertility study in male rats, a GLP fertility and early embryonal development (FEED) study in female rats, a GLP rat embryofetal toxicity study, and a non-GLP rabbit embryofetal toxicity extended dose range-finding study were conducted in order to elucidate effects on the developing fetus. No studies to investigate pre- and postnatal development have been conducted. This was considered acceptable

considering the adverse developmental effects of alpelisib shown in rats and rabbits with no safety margin. A standard genotoxicity battery was performed. Given the potential long-life expectancy, a 2-year rat carcinogenicity study was conducted.

The non-clinical overview has been updated with this new MAA and results of the 2-year rat carcinogenicity study, an updated ERA following the revised guideline adopted in sept 2024 and new calculations of the multiple of exposure (safety margins) were provided.

4.2. Analytical methods

The ADME studies were conducted using ^{14}C-radiolabeled and non-radiolabeled alpelisib. Toxicokinetic studies were performed using non-radiolabeled alpelisib.

Concentrations of radioactivity in blood, plasma, bile, urine, feces, carcass, cage wash and dose solutions were measured by liquid scintillation counting (LSC). The radioactivity concentrations in organs and tissues were determined by quantitative whole-body autoradiography (QWBA) and quantified by comparative densitometry.

Alpelisib free base was quantified by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) in plasma samples of mouse, rat, rabbit, dog and human. Metabolite BZG791 was quantified in plasma samples of rat and dog. 15N13C5-alpelisib and 15N13C5-BZG791 were used as internal standards for bioanalytical quantification of alpelisib and BZG791, respectively.

Validated methods were used for quantification of alpelisib and BZG791 in rat and dog plasma and alpelisib in rabbit plasma. The limit of quantification (LOQ) was 1.0 ng/mL for alpelisib and 0.950 ng/mL for BZG791, using 0.1 mL of either rat or dog plasma in 4-week toxicity studies; 1.0 ng/mL for alpelisib using 0.05 mL of either rat or dog plasma in the 13-week toxicity studies and 1.0 ng/mL for alpelisib using 0.02 mL of rabbit plasma in the embryofetal development dose range finding study.

Stability of alpelisib was assessed at a concentration of 100 ng/mL in blood and plasma of mouse, rat, dog and human. Spiked blood and plasma samples were incubated at 37°C for up to 7 and 30 hours, respectively. No relevant degradation was observed in either matrix.

Metabolite concentrations and metabolite patterns, *in vitro* in hepatocytes, and in plasma, urine, feces and bile samples of rat, dog and human ADME studies were obtained by HPLC with either offline or online radioactivity detection. Metabolite structure elucidation was carried out using HPLC-MS or HPLC-MS/MS and, whenever possible, by comparison to reference standards.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

The pharmacology package submitted is identical than the one submitted in the first submission of the MAA in 2022. No additional study and no additional literature reference were submitted.

In vitro activity

In vitro studies with alpelisib appears to show that alpelisib is ɑ specific class I PI3K inhibitor.

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

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

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

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

In vivo **activity**

Alpelisib showed a dose and time-dependent inhibition of the PI3K/Akt pathway (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice and rats. In Rat1-myr-p110a tumour-bearing nude mice, alpelisib induced dose dependent anti-tumour effect at oral doses of 12.5, 25 and 50 mg/kg for up to 8 days which correlated with inhibition of Akt phosphorylation. Alpelisib appears to produce dose-dependent anti-tumour effect when compared to the vehicle treated group in the *in vivo* BT-474 luminal B breast tumour bearing mice model which harbours a K111N mutation in PIK3CA and an ERBB2 amplification.

Results described in one newly submitted published study (Venot et al 2018) revealed that alpelisib inhibition of the PI3K pathway resulted in the prevention of the onset of PROS lesions such as a reduction in tumour volume in a mouse model of PROS/congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES). However, although the tested dose (50 mg/kg) was largely in excess in comparison to the clinical dose, histological analysis revealed minor changes of tissue abnormalities detected by magnetic resonance imaging. Therefore, the submitted non-clinical proof-of-concept is not convincing.

4.3.1.2. Secondary pharmacodynamics

No new study was submitted, the secondary pharmacodynamic studies submitted were already assessed in the alpelisib application for breast cancer (PIQRAY). This is acceptable.

The potential for off-target pharmacology activity of alpelisib was also evaluated against 143 GPCRs, transporters, ion channels, nuclear receptors and enzymes, in binding assays. At a concentration of 10 µM, alpelisib exhibited >50% inhibition against 2 targets, the adenosine Ad3 and serotonin 5HT2A receptors. The IC_{50} values for these receptors were 2.25 µM (Ki=2.15 µM) and 6.7 µM (Ki=4.6 µM), respectively. The results for 5HT2A receptor were found with batch NX-1 but were not confirmed with batch NX-2. Weaker pharmacology activity was also found on the adenosine Ad1 receptor (15 µM, Ki=13 µM) and the phosphodiesterase PDE4d (13 µM). IC_{50} values found are all around 1000 fold or higher than the IC_{50} values found for PI3Kα.

The PI3K/Akt pathway and more specifically p110α, plays a significant role in glucose metabolism, particularly by mediating glucose transport into adipocytes and muscle tissues. The effects of alpelisib on glucose uptake were assessed in 3T3-L1 differentiated cells. The IC_{50} value obtained in this study was 169±75 nM. The impact of treatment with alpelisib on glucose homeostasis was assessed in more detail in mice and revealed that insulin plasma levels increased proportionally with alpelisib plasma concentrations, while blood glucose levels were maintained close to normal up to 20 µmol/L of alpelisib. However, above 20 µmol/L, an alpelisib concentration-dependent glucose increase was observed which led to hyperglycaemia despite insulin plasma level elevation.

4.3.1.3. Safety pharmacology

Several stand-alone safety pharmacology studies were conducted. Additionally, cardiovascular system safety pharmacology endpoints were incorporated into study designs for the pivotal repeat-dose toxicity in dogs.

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

Alpelisib had an IC_{50} value of 9.4 µM in the hERG assay corresponding to approximately 4.2 µg/ml free drug. Based on Cmax values derived from the PopPK model rather than the Cmax obtained in study EPIK-P2 (more conservative approach), the exposure multiples were calculated at 21- fold in adults and 31-fold in children.

Although, no treatment-related ECG effects in dogs were noted within 2 and 4 and 13-week repeated oral dose toxicity studies up to 90 mg/kg/day and rising-dose study up to a dose of 180 mg/kg/day, an *in vivo* telemetry study in dogs showed an elevated blood pressure, at doses starting from 5 mg/kg, which is lower than the exposure in adult patients at the recommended dose of 250 mg/kg.

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

4.3.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were performed. This is acceptable.

4.3.2. Pharmacokinetics

The pharmacokinetic package submitted is identical to the one submitted in the first submission of the MAA in 2022. No additional study and no additional literature reference were submitted.

4.3.2.1. Absorption

The animal PK profile of alpelisib was characterized and assessed in the previous MAA for PIQRAY. No additional studies are submitted in the Vijoice submission. This is acceptable. Data obtained in these studies are summarized below.

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

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

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

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

In pregnant rats and rabbits, exposure to alpelisib increased more than dose proportional at lower doses (8 fold between 3 and 10 mg/kg in rats and 6 fold between 3 and 15 mg/kg in dogs) and approximately dose proportionally at higher doses (3 fold between 10 and 30 mg/kg in rats and 1.7-fold between 15 and 25 mg/kg in dogs).

4.3.2.2. Distribution

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

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

4.3.2.3. Metabolism

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

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

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

4.3.2.4. Excretion

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

4.4. Toxicology

The toxicology package submitted is nearly identical than the one submitted in the first submission of the MAA in 2022. The results of 2-year rat carcinogenicity study are now available and are added in this new submission. In addition, new multiples of exposures are updated with results of pop PK parameters in PROS patients. Previously, the multiples of exposure were based on exposures in cancer patients, but data in targeted population is now preferred. Margins of safety are still below 1 with the new human PK parameters and do not affect the conclusion from animal studies.

4.4.1. Single-dose toxicity

The single dose study in Beagle dogs was used for dose setting purposes for the repeated dose studies. In the study a slight to moderate body weight loss was seen at the lowest dose at ≥ 10 mg/kg and slightly to severely reduced food consumption as well as diarrhoea was seen at ≥ 90 mg/kg. No treatment-related effects on electrocardiographic parameters were seen, and no deaths occurred at any dose level.

4.4.2. Repeat-dose toxicity

<u>In rats</u>

Repeat-dose toxicity studies in rats were conducted with alpelisib for 2 weeks, 4 weeks with a 4-week recovery period and 13 weeks with an 8-week recovery period.

At doses above 50 mg/kg in the 4-week rat study, severe toxic effects related to intestinal toxicity were seen, resulting in marked reduction in food intake with associated body weight loss and necessitated early sacrifice of 6 animals. The effects led to reduction in dose level from 80 mg/kg to 30 mg/kg.

There is an overlap of the effects and toxicity target organs across the three studies in rats at doses up to 50 mg/kg and the following was observed: reduction of body weight development; effects on glucose and insulin levels seen correlated with cytoplasmic atrophy in the islet cells in the pancreas; lymphoid depletion of spleen and thymus combined with effects on hemo- and lymphopoiesis. These effects suggest a relationship with the pharmacological activity of alpelisib as a phosphoinositide 3-kinases (PI3K) inhibitor which inhibits cell proliferation in certain tissues. Furthermore, effects on the estrus cycle associated with uterine atrophy were observed in the 4-week study in rat pointing towards potential effects on female fertility. In general, the changes observed macro- or microscopically were fully reversible or showed a tendency toward reversibility.

No NOAEL was determined in the 4-week study. Indeed, at the lowest test dose (10 mg/kg/day), toxic adverse were observed. This point was previously discussed during PIQRAY MAA and the use of 10 mg/kg/day as NOAEL was discarded.

The use of 2 mg/kg/day as NOAEL in 13-week study was supported. Based on the calculated safety margins (<1), adverse events in rats occurred at therapeutic plasma levels or below.

In dogs

Repeat-dose toxicity studies in dogs were conducted with alpelisib for 2 weeks, 4 weeks with a 4-week recovery period and 13 weeks with a 4-week recovery period.

In the 2-week dog study, both animals had to be euthanized during the 1st week of treatment at 90 mg/kg/day due to bad health conditions. Both animals showed decreased motor activity and severely reduced body weight gain and food consumption.

There is an overlap of the effects and toxicity target organs across the three studies in dogs at doses up to 30 mg/kg and the following was observed, which also correlates with the effects observed in rat: reduction of body weight development; effects on glucose and insulin levels indicative of altered glucose metabolism; lymphoid depletion in several lymphoid tissues; inflammatory reaction in several organs; atrophic changes in the GI tract. These effects suggest a relationship with the pharmacological activity of alpelisib as a phosphoinositide 3-kinases (PI3K) inhibitor which inhibits cell proliferation in certain tissues. Furthermore, atrophy in the prostate was observed in the 4-week study in dogs pointing towards potential effects on male fertility. In general, the changes observed macro- or microscopically were fully reversible or showed a tendency toward reversibility.

In 4-week study in dogs, no NOAEL was determined. In 13-week study, NOAEL was set up at the dose of 1 mg/kg/day. Based on the calculated safety margins (<1), adverse events in dogs occurred at therapeutic plasma levels or below.

4.4.3. Genotoxicity

Standard battery for alpelisib were performed according to the ICH S2 guideline, including test for gene mutations, chromosomal aberrations *in vitro* and an *in vivo* micronucleus assay integrated in the 13-week oral repeated-dose rat study in rats. Alpelisib was negative *in vitro* and *in vivo* studies. Toxicokinetics were not performed at week 4 at the time of the blood collection; however, rat exposures after 20 mg/kg/day (highest tested dose) were measured at D1 and D75 in this 13-week study and rat exposures after 10 and 30 mg/kg/day administration were measured at W4 in the 4-week study. The

multiples of 2.6 and 5 (based on AUC in adult and paediatric patients, respectively) included in the SmPC section 5.3 is considered acceptable.

4.4.4. Carcinogenicity

A 2-year carcinogenicity in rats was performed at dose levels of 1, 2 and 4 mg/kg/day. No increase in neoplastic findings was noted in male or female rats administered up to the highest tested dose of 4 mg/kg/day. The highest tested dose (4 mg/kg/day) is corresponding to 0.6 to 0.3 times the recommended doses of 50 mg and 250 mg in pediatric and adult patients.

The relevance of this study to characterize the carcinogenicity potential in humans is limited given the low multiples of exposure.

To complete the assessment of the carcinogenicity potential the Applicant has detailed the six factors mentioned in the current ICHS1B (R1) guideline and conclude that based on the available non-clinical data, there is no indication of an increased carcinogenic risk for alpelisib. The intended indication is outside the scope of ICH S9 guideline, therefore a 26-week carcinogenicity study in transgenic mice is expected in the non-clinical package.

Currently, a carcinogenicity study in mice will be conducted and results will be provided Q4 2027 (as a post-approval measure). The design of this study and especially the dose selection was not detailed yet as the 4-week DRF study in Tg mice is currently ongoing.

4.4.5. Developmental and reproductive toxicity

To evaluate the potential effect of alpelisib on reproductive potential and embryofetal development, male and female fertility and embryofetal development GLP-compliant studies were conducted in rats. In addition, a non-GLP rabbit embryofetal toxicity extended dose range-finding study was performed.

Data from fertility and repeat-dose toxicity studies suggest that alpelisib may impair human male and female fertility, as indicated already in SmPC section 4.6. In males, adverse effects on prostate and seminal vesicles weight and histology were reported in rats and/or dogs. In females, there were adverse effects on reproductive performance leading to a decrease in live embryos in the rat fertility study with additional findings on estrous cycles and reproductive organs in toxicity studies. In general, these effects were observed at exposure levels close to those in human patients and an acceptable safety margin could not be derived.

In the rat embryofetal development study, adverse developmental findings including teratogenicity (mainly bent scapula and thickened or bent long bones) and fetal toxicity (decreased fetal weight, dilated brain ventricle, delayed ossification) were noted at 10 mg/kg/day corresponding to systemic exposure levels within clinical exposure. At the highest dose of 30 mg/kg/day (4.9-fold clinical exposure), embryolethality resulted in 100% postimplantation loss (all early resorptions). In the non-GLP preliminary/dose range-finding study conducted in rabbits, adverse developmental effects consisted mainly in malformations mostly related to the tail and head, and embryo-foetal lethality; no adverse developmental finding was noted at the low dose of 3 mg/kg/day (1.3-fold clinical exposure), however this should not be viewed as a definitive developmental NOAEL in that species due to the nature of the study and absence of fetal skeletal examination.

The applicant also submitted a programme of dose range-finding and definitive juvenile animal studies (JAS) conducted in rats from 7 days postnatal (PND7). In the dose range-finding study, administration of alpelisib was not tolerated at 50 mg/kg/day with mortality and adverse body weight loss and clinical signs noted from PND12, leading to dose reduction to 35 mg/kg/day from PND 14-16 and subsequent

group termination on PND 16 to 18. In the remaining groups dosed at 10/20 and 20/40 mg/kg/day (doses adjusted on PND30), body weights and body weight gains were reduced and no drug-related clinical signs or necropsy findings were observed. In the definitive study, alpelisib administered from PND7 at 20 mg/kg/day induced lower body weights, reduced body weight gains, and reduced food consumption. Sexual maturation was delayed in males and femur lengths were decreased in both sexes at this dose level. In addition, adverse and non-reversible histopathological findings were observed in the kidneys (minimal to moderate increased vascular/perivascular extracellular matrix deposition in small vessels and minimal to moderate tubular degeneration/regeneration in the renal papilla and medulla) and were associated with increased blood urea nitrogen at the end of the 14-week recovery period. These kidney effects are likely not relevant to humans aged 2 years and above as human renal maturation is completed in this population and taking into consideration the rat vs. human differences in postnatal renal development. In addition, a review of available clinical safety data (dated 12 Sept. 2025) did not establish a clinical relevance of these kidney findings in the target paediatric population. Overall, the NOAEL was determined at 6 mg/kg/day associated with exposure levels lower than those in paediatric patients at the recommeded dose of 50 mg/day, with effects at 20 mg/kg/day seen at exposure levels of 2- to 4-fold those in paediatric patients.

4.4.6. Toxicokinetics and exposure margins

It is noted that there are no safety margins at the recommended clinical doses. Animal/human multiples of exposures were calculated based on human PK parameters from popPK model (2025) built from PROS patient data, although some measured data were available. It is however acceptable given the margin of error is below 5%; indeed, after treatment at 250 mg in adults, the predicted AUC was to be 19 741 ng.h/ml by the used model PopPK and the observed AUCss at 125 mg was 9 460 ng.h/ml (i.e. 18920 ng.h/ml). However, in children (2-<6 years of age) new predicted AUC values are expected, therefore the table 4-5 of the non-clinical overview should be updated once new data become available from the EPIK-P4 study.

4.4.7. Local tolerance

No sensitizing potential was observed in the sensitizing study and no skin irritation or corrosive potential was observed in the irritation/corrosion study.

4.4.8. Other toxicity studies

Metabolite

The most prominent plasma metabolite in human was BZG791 which represented 26.7% of total 14C AUC (measured in adults). No paediatric PK parameters are available to discuss BZG791 exposures in children; however, since alpelisib could be administrated in children starting from 2-years old and metabolic pathways are considered mature at this age, BZG791 exposure in children is not expected to be a cause of concern. This metabolite results from amide hydrolysis and is also present in rat (7.6 %) and dog (< 5.1%). Dedicated primary pharmacodynamics and genotoxicity studies with BZG791 (Ames test and *in vitro* micronucleus assay) were performed and raised no concern; BZG791 had no relevant contribution to the total pharmacological activity in human and dedicated *in vitro* genotoxicity studies were negative. BZG791 level exposure was measured only in alpelisib 4-week studies in rat and dog: human exposure to this metabolite was covered by the rat and in dog as more than 0.5-fold the clinical exposure range. Since no increase or decrease of BZG791 was observed between D1 and D30 in the 4-week rat study, it could be considered that exposure in rat for longer administration period (e.g. 13

weeks) will be similar. Therefore, the metabolite BZG791 was adequately assessed in the repeated dose toxicology studies according to the requirements described in ICH guideline M3. As alpelisib exposures in 2-year carcinogenicity are considered insufficient to characterize the carcinogenicity potential, therefore the same conclusion could be drawn for the metabolite as it is expected to be at around 0.5 in rat, therefore an assessment of BZG791 carcinogenicity potential in humans is also requested (OC in carcinogenicity part).

Impurities

A number of identified impurities were evaluated in the Ames test as well as referenced from published literature. Discussions of genotoxic classification appear to be adequate. Measures to ensure adequate control of the genotoxic impurities are shown in the quality part of the assessment.

Four studies on genotoxic potential of impurities were conducted in compliance with GLP. Six studies were not GLP-compliant. Three of the impurities were tested positive in the non-GLP AMES tests. Three impurities were tested negative in non-GLP studies (study 0812020, 1212509 and 1712518 respectively). The TTC limit for a maximum treatment duration of 10 years to lifetime and maximum daily dose of 250 mg alpelisib drug substance against the requirements of the ICH M7 guideline has been recalculated, providing a TTC limit of 6 ppm for Class 2 or Class 3 impurities.

Phototoxicity

Absorption studies with alpelisib showed absorption between 290 – 700 nm (peak at 314 nm) with a molar extinction coefficient above the guideline limit of 1000 L/mol/cm (i.e. 1880 L/mol/cm). Alpelisib was tested as recommended in ICH S10 guideline, *in vitro* 3T3 NRU phototoxicity test was conducted (one non-GLP and one GLP compliant). No phototoxicity potential for alpelisib was identified up to 1000 µg/mL (the maximum recommended concentration according to the OECD guideline).

Investigative studies (skin toxicity)

In a non-GLP study, insulin receptor function and regulation of glucose metabolism was investigated *in vivo* in mice. Results indicated insensitivity/resistance after single and repeated exposure. The results of the study are considered supportive of the effects already seen in repeat dose toxicity studies where effects on glucose metabolism and insulin levels have already been shown.

Follow-up rat studies to investigate mechanism of skin rashes confirmed the results already obtained in 4-week oral (gavage) investigative skin toxicity study in female Brown Norway rats which was previously assessed in PIQRAY procedure. The mechanism of skin toxicity needs to be further investigated, however it can be concluded that alpelisib induced a T cell-mediated hypersensitivity reaction and some markers of the hypersensitivity reaction were changed as early as 1 day after treatment initiation.

4.4.9. Ecotoxicity/environmental risk assessment

The applicant provided an Environmental Risk Assessment in accordance with the EMA guidance (EMEA/CHMP/SWP/4447/00, corr. 1).

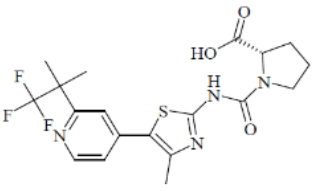
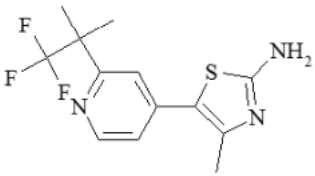
Phase I of the ERA showed that the predicted environmental concentration in surface water (PECsurfacewater) was higher than the threshold value of 0.01 µg/L. Thus, a Phase II ERA was triggered. The outcome of the Phase II risk assessment indicates no noteworthy risk potential for surface waters,

groundwater, microorganisms in sewage treatment plants, and sediments. Alpelisib is not a PBT substance, according to the criteria outlined in the EMA guidance.

Overall, the new indication leads to an increase in environmental exposure, however, alpelisib is not expected to pose a risk to the environment.

Table 6: Summary of main study results: Phase I and II

Substance (INN/Invented Name): Alpelisib			
CAS-number (if available): 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 (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF_{KLg}	1.71 L/Kg (low dose) 2.05 L/kg (high dose)	Not B
Persistence	DT50 Values are derived from the OECD 308 study below and have been recalculated to 12°C	$DT_{50\ (sediment,\ 12\ ^oC)}$ = 186 d $DT_{50\ (total\ system,\ 12\ ^oC)}$ = 138 d	vP
Toxicity	NOEC or CMR		T
PBT-statement:	Alpelisib is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw,\ default}$	1.5	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption 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 301	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%, max. 10.6%/ 36.9%	DT50s at 12ºC At day 7 At test end At test end

		 TP2 = max 11.5 / 38.6%  DT_{50} TP1: NA DT_{50} TP2: NA			At test tend At day 32 TP1: BZG791 in water and sediment (decreasing) At test end TP2 = 4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-amine in sediment (increasing)
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**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					
Bioaccumulation/ *Oncorhynchus mykiss*	OECD 305	BCF_{Kg} BCF_{Kg}	1.20 1.43	L/kg_{ww} L/kg_{ww}	%lipids: 3.5%
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	64	mg/kg_{dw}	Emergence ratio and development

Alpelisib is not a PBT substance or vPvB substance. While it does fulfil the criteria for persistence, it does not show any noteworthy bioconcentration in fish. Alpelisib is not expected to pose a risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Alpelisib in combination with fulvestrant was approved by the EMA on 27-Jul-2020 under the trade name of Piqray for the treatment of post-menopausal women, and men, with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy. A MAA for CMA was initially submitted to EMA for Vijoice (alpelisib) in Jun-2022 for the treatment of patients with PROS but was subsequently withdrawn in Oct-2023 as

prospective clinical data from Study EPIK-P2 could not be provided within the procedural timelines. All the non-clinical studies included in the current MAA were previously submitted and reviewed in the context of either the Piqray MAA and/or the previously submitted Vijoice MAA except for a 2-year rat carcinogenicity study which has been recently evaluated in a Piqray variation procedure EMEA/H/C/004804/II/263396. A re-calculation of the pre-clinical exposure margins has been submitted in this MAA.

Pharmacology

Primary pharmacodynamics studies

Alpelisib (BYL719) potently inhibits both wild type and mutated forms of p110α ≥ 50x compared to inhibition of the β, δ, and γ isoforms of PI3K. In vitro, alpelisib showed selectivity towards cell lines harboring a PIK3CA mutation. In vivo studies showed that alpelisib produced a dose-dependent inhibition the PI3K/Akt pathway and exhibited significant antitumor effects in p110α-mutant xenograft models. Oral administration reduced Akt phosphorylation and tumor growth in multiple breast cancer models.

In a mouse model of PROS/congenital lipomatous overgrowth syndrome (CLOVES), inhibition of the PI3K pathway with alpelisib prevented the development of PROS lesions such as a reduction in tumour volume. However, despite the use of a high dose (50 mg/kg) in comparison to the clinical dose, histological analysis revealed only minor improvements in tissue abnormalities detected by magnetic resonance imaging. As a result, the non-clinical proof of concept based on this animal model was not considered convincing when submitted as part of the MAA for Vijoice in Jun-2022. As was the case then, clinical efficacy data are expected to supersede non-clinical PD findings in the overall assessment, and no additional non-clinical study will be requested.

Secondary pharmacodynamics studies

Alpelisib shows no significant activity against a wide range of targets in binding assays. In all species investigated, alpelisib interfered with glucose/insulin homeostasis, evident as hyperglycaemia or hyperinsulinemia. In addition, inhibition of VEGF signalling and neovascularisation by PI3K inhibitors has been associated to embryofetal toxicity and developmental abnormalities in pregnant animal studies.

Safety pharmacology studies

In vitro hERG studies showed that alpelisib did not significantly inhibit hERG current at 10 µM in screening assays. In a GLP-compliant assay, alpelisib inhibited hERG with an IC50 of 9.4 µM (4.2 µg/mL), 21-fold and 31-fold higher than the estimated maximum (peak) plasma concentration of unbound alpelisib in humans at the recommended maximum alpelisib adult and paediatric doses of 250 mg/day (adult) or 50 mg/day (ages 2 to 5 years), respectively. No relevant electrophysiological effect was seen in dogs.

In a single-dose non-invasive telemetry study in dogs up to 180 mg/kg, no relevant electrophysiological effect was seen, in agreement with electrocardiographic readouts obtained in the repeated-dose toxicity studies in dogs. However, in a single dose invasive telemetry study in dogs at doses up to 30 mg/Kg, an increase in systolic and diastolic blood pressure was seen at exposure levels below clinical levels, in the absence of any electrophysiological abnormality. As a consequence, a decrease in heart rate was observed.

Pharmacokinetics

All non-clinical pharmacokinetic data included herein were previously submitted and assessed as part of the MAA for Piqray.

Plasma protein binding of alpelisib was moderate in mouse, rat, dog and human, with unbound fractions (fu,p) ranging from 8.76% to 10.8% (10.8 in humans), and no significant species differences or concentration dependence observed. In humans, the metabolite BZG791 exhibited high plasma protein binding (fu,p 3.6%) without evidence of concentration dependency.

The main metabolic pathway observed in rat, dog and human was amide hydrolysis to BZG791 (M4), with minor contributions from oxidative metabolism and glucuronidation. Unchanged alpelisib was the major plasma component across species. In humans, BZG791 was the main metabolite (26.7% of total 14C AUC), with exposure adequately covered in rat toxicology studies. BZG791 had no relevant contribution to total pharmacological activity in human.

Toxicology

All toxicity studies submitted in this application were already evaluated to support the PIQRAY application for the breast cancer indication, with the exception of the rat male and female fertility studies (studies 2070119 and 2080120) and follow-up rat studies to investigate mechanism of skin rashes (studies 1770766 and 1870156), which were assessed during the alpelisib initial MAA submitted in Jun-2022 for the treatment of PROS and withdrawn in Oct-2023. Therefore, the only new toxicity study submitted with this application is a 2-year rat carcinogenicity study which has been recently evaluated in the Piqray variation procedure (EMEA/H/C/004804/II/263396).

Repeated-dose studies (up to 13 weeks of duration) were performed in rats and dogs. Hematopoietic, lymphopoietic, reproductive and gastrointestinal systems, the glucose and lipid metabolisms, skin, adnexal tissues, teeth, bones, kidneys and eyes were identified as systems affected by treatment with alpelisib. In addition, degenerative effects seen in incisors and some growth plates of bones in rats were noted. Since this could be of relevance for the paediatric population, these effects are reflected in SmPC section 5.3.

When NOAELs were observed in repeated-dose toxicity studies, which was the case in the 13-week toxicity study in rats at 2 mg/kg/day as well as in the 13-week dog study at 1 mg/kg/day, associated exposures were generally at or below the clinically relevant plasma levels at the recommended human dose levels.

Alpelisib was not genotoxic in *in vitro* assays and in an *in vivo* rat micronucleous test at clinically relevant doses.

Alpelisib was not carcinogenic in a 2-year carcinogenicity study conducted in rats when administered by daily oral gavage at doses up to 4 mg/kg (approximately 0.3 times the clinical exposure in patients at the highest recommended dose of 250 mg/day based on AUC). The relevance of this study to characterize the carcinogenicity potential in humans is limited given the low multiples of exposure. There is no indication of an increased carcinogenic risk for alpelisib based on a weight-of-evidence approach. The carcinogenicity assessment will be complete with a 26-week transgenic mouse study, dose selection is currently ongoing with a 4-week DRF study. The result of pivotal study will be available Q4 2027. The results of the study will be submitted post-approval as a post-authoristaion measure (PAM). The Applicant is invited to measure BZG791 in the planned 26-week carcinogenicity study in Tg mice and discuss the exposure margins of the parent and its major metabolite obtained in this study.

The package of reproductive and developmental toxicity studies is overall acceptable. The results of fertility studies in rats and repeat-dose toxicity studies in rats and dogs suggest that alpelisib may impair human male and female fertility, as indicated in SmPC section 4.6.

Embryofoetal development studies in rats and rabbits (DRF) have shown that oral administration of alpelisib during organogenesis induced embryotoxicity, fetotoxicity and foetal malformations starting at

exposures within those in humans at the highest recommended dose in adult patients, indicating potential clinical relevance. In that context, the absence of pre- and postnatal development study is acceptable.

No juvenile animal study (JAS) was conducted with alpelisib in patients from 2 to 18 years of age. In rat repeat-dose toxicity studies, degenerative effects seen in incisors and growth plates of bones were noted and could be of relevance for this paediatric population considering the low or inexistent safety margin. Effects on sexual organs and estrous cyclicity in toxicity studies were also reported. Therefore, growth, bone/dental development and puberty are assessed in PROS studies (ongoing and planned) and included in the RMP as missing information. To support development in patients below 2 years with lymphatic malformations associated with a PIK3CA mutation, a JAS was performed in rats. The applicant informed on salient findings, highlighting effects on femur length and delayed male sexual maturation as well as non-reversible kidney findings (increased vascular/perivascular extracellular matrix deposition in small vessels and tubular degeneration/regeneration in the renal papilla and medulla) at the high dose of 20 mg/kg. At this dose, exposure levels were 2.2- to to 4.2-fold higher than exposure predicted for a reference paediatric patient with PROS aged 2 years treated at 50 mg QD. As regards to effects on kidney, the applicant explains that no impact on benefit-risk profile is foreseen on patients ≥ 2 years as human renal maturation is completed in this population and taking into consideration the rat vs. human differences in postnatal renal development. Accordingly, a review of available clinical safety data performed by the applicant (dated 12 Sept. 2025) does not currently establish a clinical relevance of these kidney findings in the target paediatric population. As regards the effects on bone (decreased femur length) and delayed male sexual maturation, the applicant considers that they were likely secondary to decreased body weight gain and reduced food consumption. As it was not unequivocally demonstrated that these findings are fully mediated by treatment-related body weight reduction, a direct treatment-related effect cannot be excluded.

No sensitizing potential was observed in the sensitizing study, and no skin irritation or corrosive potential was observed in the irritation/corrosion study.

Toxicokinetics/Interspecies comparison

Alpelisib systemic exposure ratios were calculated based on popPK modeling of PK data from patients with cancer and PROS. The steady-state AUC0-24h at the recommended maximum dose levels were then 19,741 ng.h/mL (adult treated with 250 mg), 18,887 ng.h/mL (6-year-old treated with 125 mg), and 10,246 ng.h/mL (2-year-old treated with 50 mg). It is noted that there are no safety margins at the recommended clinical doses. Table 4-5 of the Non-clinical Overview should be updated once new data become available from the EPIK-P4 study.

Other toxicity studies

An in vitro phototoxicity test on the mouse Balb/c 3T3 fibroblast cell line did not identify a relevant phototoxicity potential for alpelisib.

Regarding the impurities, a TTC limit of 6 ppm for Class 2 and Class 3 impurities has been calculated for a maximum treatment duration of 10 years to lifetime and a maximum daily dose of 250 mg.

4.5.2. Conclusions

For the ERA, the new indication leads to an increase in environmental exposure however, alpelisib is not expected to pose a risk to the environment.

From a non-clinical point of view, this application is approvable.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

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

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table 7: Tabular overview of main clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
CBYL719F12002 (EPIK-P1)	Status: Completed Retrospective study Treatment start date: 23 Sep 2019 Total enrolment: N= 57 (18 adult patients ≥ 18 years and 39 paediatric patients 2-17 years)	Site-based, retrospective, non-interventional, medical chart review Patients ≥ 2 years of age with severe or life-threatening PROS who received alpelisib as part of a compassionate use program	Adults (≥ 18 years): alpelisib dose of 250 mg in the fed state q.d. (FCTs), administered orally Paediatric patients (2 to 17 years): alpelisib dose of 50 mg in the fed state q.d. FCTs, administered orally	Adult or paediatric patients ≥ 2 years of age with a physician confirmed/documented diagnosis of PROS and with documented evidence of a mutation in the PIK3CA gene[1] Patient's condition was assessed by the physician as severe or life threatening and treatment was deemed necessary[1] Patients who were treated with at least one dose of alpelisib, initiated on or before 23 Sep 2019 (i.e. at least 24 weeks before the cut-off date of the 09 Mar 2020) Patients with a medical chart history available during enrolment in the MAP. Patients (in case of paediatric patients

				assent and/or parent/guardian consent) consented to participate in the study (as required by local ethics regulations). No exclusion criteria
CBYL719F12401 (EPIK-P3) Retrospective period Follow-up of the EPIK-P1 study	Status: Completed[2] Start date: 27-Jan-2022 Total enrolment: N=48 (14 adult patients ≥18 years and 34 paediatric patients 2-17 years at the start of EPIK-P1)	Multicentre, open-label study Patients ≥ 2 years of age with severe or life-threatening PROS who were previously enrolled in EPIK-P1 continued to receive treatment with alpelisib after the EPIK-P1 cut-off date, and enrolled in the retrospective period of EPIK-P3	Same as EPIK-P1	Same as EPIK-P1
CBYL719F12401 (EPIK-P3)/ Prospective period	Status: Ongoing (enrolment completed) Start date: 27-Jan-2022 Total enrolment: N= 40 (9 adult patients ≥18 years and 31 paediatric patients 2-17 years of age at the start of EPIK-P1)	Multicenter, open-label study. Patients ≥ 2 years of age with severe or life-threatening PROS who were previously enrolled in EPIK-P1, continued to receive treatment with alpelisib after the EPIK-P1 cut-off date, and enrolled in the prospective period of EPIK-P3	Same as EPIK-P1	Patients who had previously participated in EPIK-P1 and consented to any study related screening procedures being performed. Note: Two separate ICFs must be signed, one for each part of the study, i.e., the retrospective and prospective periods, as per local regulations. Patient was treated with at least one dose of alpelisib after the data cut-off date for EPIK P1 (i.e., 09 Mar 2020): If patients discontinued treatment for safety reasons prior to the first visit for the prospective period of the current study and if the treatment cannot be restarted, but they provided consent for the retrospective period, only the retrospective data were abstracted. If patients discontinued treatment for any other reason, including worsening of disease, prior to the first visit for the prospective period of the current study, and

				they provided consent to restart treatment as considered beneficial by the Investigator, they were eligible for both the periods.
CBYL719F12201 (EPIK-P2)	Status: Ongoing (enrolment completed in Group 1, 2, 4 and 5; enrolment ongoing in Group 3) [3] Start date: 19-Apr-2021 Total Enrolment: N= 188 **Group 1** (n=81; Alpelisib: 54 and Placebo: 27 of whom 26 patients transitioned to alpelisib after double-blind period) **Group 2** (n=84; Alpelisib: 56 and Placebo: 28 of whom 26 patients transitioned to alpelisib after double-blind period) **In Group 4** (n=7) **In Group 5** (n=16)	Phase II double-blind study with an upfront 16-week randomized, placebo-controlled period, Patients ≥ 2 years of age with PROS irrespective of disease severity	**Group 1** (≥ 18 years): starting alpelisib dose/matching placebo of 125 mg in the fed state q.d. (FCTs)[4], administered orally **Group 2** (6 to 17 years) and **Group 4** (2 to 5 years): starting alpelisib dose of 50 mg/matching placebo (for Group 2) in the fed state q.d. (FCTs), administered orally **Group 5** (6 to 17 years): starting alpelisib dose of 125 mg in the fed state q.d. (FCTs) [4], administered orally	The study included male or female patients aged 2 years and older, categorized into five groups based on age. Eligible patients had a diagnosis of PROS with symptomatic/progressive overgrowth and measurable PROS-related lesions. Those who had previously received systemic treatment for PROS could enter the study. Additionally, patients needed documented evidence of somatic mutations in the PIK3CA gene, tested in certified local laboratories. Karnofsky (in patients > 16 years old at study entry)/Lansky (≤ 16 years of age at study entry) performance status index ≥ 50. Details in Section 3.3.3

1 Inclusion criteria for MAP enrolment in EPIK-P1(assessed at the time of alpelisib initiation)
[2] For EPIK-P3, a single data cut-off date for all patients was not applicable due to the design of the study. There was a protocol specified end of the retrospective period for each patient. 04 Aug-2022 was the last patient first visit (LPFV) in the prospective period
3 Only Groups 1, 2, 4, and 5, which are included in the primary and interim analysis Clinical study report (CSR) are discussed in this table.
4 Patients in Groups 1 and 5 were not treated at doses that are recommended in the label; detailed information for these groups is provided in [EPIK P2 primary analysis CSR] and [EPIK-P2 interim CSR-25-Sep-2024]
5 The treatment of adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PROS who require systemic therapy
Source: BYL719 PROS Clinical overview Table 1-1

5.2. Clinical pharmacology

Alpelisib is an orally available α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds.

In Europe, Alpelisib was approved on 27-Jul-2020 under the brand name of Piqray.Alpelisib in combination with fulvestrant is indicated for the treatment of post-menopausal women, and men, with

hormone receptor (HR)-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following an endocrine-based regimen.

A Marketing Authorisation Application of alpelisib for the treatment of patients with PROS was initially submitted to the EMA in June 2022. However, the application was withdrawn in October 2023, as the data requested by the CHMP could not be provided within the procedural timeframe.

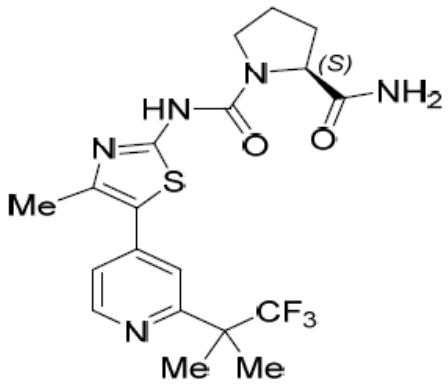
In the current re-submission of the MAA, the applicant seeks a marketing authorization for alpelisib as monotherapy for the treatment of adult and paediatric patients aged 2 years and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy. The recommended dosing regimen is:

- 250 mg orally, taken once daily (qd) in adult patients, and
- 50 mg orally, taken qd in paediatrics patients (2 -<18 years) with a dose increase to 125 mg that should be considered in children ≥6 years old for response optimization after 24 weeks of treatment

Two pharmaceutical forms are proposed for the PROS indication: the FCT which will be available in three strengths-50 mg, 125 mg (a new strength), and 200 mg and the 50 mg granule form. The latter provides a treatment option for patients who are prescribed the 50 mg dose and who have difficulty swallowing the FCTs.

Alpelisib has a molecular weight of 441.47 Da. The molecular formula is $C_{19}H_{22}f_3N_5O_2S$ and the chemical structure of the drug substance is presented in **Figure 2**.

Figure 2: Chemical structure of Alpelisib



An overview of the clinical pharmacology and clinical studies pertaining to PK components in healthy subjects, patients with cancer, and patients with PROS is summarised in **Table 1** below.

The fundamental ADME characteristics of alpelisib have been sufficiently characterized through clinical studies in healthy participants and cancer patients, and these data were previously evaluated and accepted within the oncology submissions. Consequently, the pharmacokinetic (PK) profile of alpelisib is well-established, as reflected in Section 5.2 of the approved SmPC of Piqray. Thus, the present report will focus exclusively on the specific PK data and analyses pertaining to the PROS indication in support of this submission under review:

- The introduction of the 50 mg alpelisib granule formulation and investigation of the granules' food effect (Bioequivalence Phase 1 **Study F12101** versus the tablet dosage form), as well as the addition of the new tablet strength 125 mg.

- The PK data from patients with PROS from the confirmatory Phase 2 **Study F12201** (referred to as **EPIK-P2**), including the first paediatric PK data for alpelisib and the first alpelisib PK data from patients with PROS
- The new Population PK (Pop-PK) analysis specifically conducted using PK data from the target population and new PK/PD and exposure-responses analyses for safety and efficacy in patients with PROS enrolled in EPIK-P2.

Table 3: Overview of clinical pharmacology studies.

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
Biopharmaceutical studies				
Study CBYL719**A2103** (Food effect & ranitidine DDI)	Single-centre, open-label, randomized, five period, ten sequence crossover study to investigate the singular and joint effect of food and the histamine H2-receptor antagonist ranitidine on the PK of oral alpelisib in healthy subjects	21 healthy subjects Male: 17 Female: 4	Single dose 300 mg Fasted & fed	AUCinf, AUClast, Cmax
Study CBYL719**X1101** (Food effect)	Exploratory, randomized, 2 period, 2 sequence crossover food effect expansion/ Japanese patients with advanced solid tumors whose tumors have an alteration of the PIK3CA gene	Total pts: 33 healthy subjects Male: 16 Female: 17 Food effect n=8 (6 completed) Male: 1 Female: 7	Repeated dose 350 mg Fasted & fed	AUC0-24, AUCinf, AUClast, Cmax
Study CBYL719**A2109** (Bioequivalence)	Single-centre, randomized, open-label, two cohort, two-period crossover study to investigate the bioequivalence between alpelisib optimized FMI tablet and FMI tablet in healthy volunteers in the fasted and fed state	Cohort 1: 34 healthy subjects (30 completed) Male: 33 Female: 1 Cohort 2: 74 healthy subjects (71 completed)	Single dose 200 mg Fasted & Fed	AUCinf, AUClast, Cmax
Study CBYL719**F12101** (Granules vs FCT BE, granules food effect)	Single-centre, randomized, open-label, three-period crossover study to investigate the bioequivalence of alpelisib granule and FCT	60 healthy subjects (48 completed) Male: 55 Female: 5	Single dose 50 mg Fasted (granules only) & fed (granules and FCT)	AUCinf, AUClast, Cmax

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
	formulations, and the food effect on alpelisib granule formulation in adult healthy volunteers			
Study CBYL719**X2104** (Bioavailability)	A Phase Ib dose escalation/randomized Phase II, multicentre, open-label study of BYL719 in combination with cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma	45 patients with recurrent or metastatic head and neck squamous cell carcinoma Male: 31 Female: 14	Single dose 300 & 400 mg (intact vs crushed FCT)	AUC0-24, AUClast, Cmax
Mass balance (hADME) human (Absorption, Distribution, Metabolism and Excretion)				
Study CBYL719**X2107** (hADME)	Single-center, open-label study to investigate the Absorption, Distribution, Metabolism and Excretion (ADME) of alpelisib in healthy subjects	4 healthy male subjects	Single dose 400 mg Fasted	Plasma alpelisib, plasma total radioactivity, blood total radioactivity: AUCinf, AUClast, Cmax, Tmax, T1/2 Plasma alpelisib: CL/F, Vz/F
Special populations study				
Study CBYL719**A2105** (Hepatic Impairment)	Phase 1, open-label, single-dose, multicentre, parallel group study to assess pharmacokinetics of and safety of alpelisib (BYL719) in patients with moderate and severe hepatic impairment (based on Child-Pugh) compared to matched healthy subjects	23 Hepatic impairment patients (6 moderate, 6 severe) + 11 healthy subjects Male: 13 Female: 10	Single dose 300 mg Fasted	AUCinf, AUClast, Cmax
Drug-drug interaction studies				
Study CBYL719**Z2102** (Everolimus DDI)	Phase Ib dose-finding, open label safety and tolerability study of the combination of alpelisib and everolimus (and exemestane) in patients with advanced solid tumours (Alpelisib as a	13 patients with advanced solid tumours dosed with everolimus and alpelisib 250 or 300 mg Male: 4	Repeated dose 250 or 300 mg q.d.Fed	AUCinf, AUClast, Cmax

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
	potential perpetrator of a CYP3A4)	Female: 9 7 patients with advanced solid tumours dosed with everolimus exemestane and alpelisib 200 mg Female: 7		
Study CBYL719**A2110** (Rifampin DDI)	Phase I, open-label, fixed sequence, two-period DDI study to investigate the effect of multiple doses of rifampin, a potent CYP3A4 inducer, on the single and repeated dose pharmacokinetics of alpelisib in healthy subjects	25 healthy subjects dosed with rifampin and alpelisib 300 mg Male: 18 Female: 7	Repeated dose 300 mg q.d. Fed	AUCinf, AUClast, Cmax
Study CBYL719**A2111** (DDIs with sensitive CYPP450 substrates)	Phase I, open-label, fixed-sequence, two-period, DDI study to investigate the effect of alpelisib on the pharmacokinetics of midazolam, bupropion, repaglinide, warfarin, and omeprazole in healthy subjects	34 healthy subjects (28 completed) Male: 25 Female: 9	Repeated dose 300 mg q.d Fed	AUCinf, AUClast, Cmax
Single agent PK studies in subjects with solid cancers				
Study CBYL719**X2101** (FIH dose ranging)	Phase Ia, multicenter, open-label dose escalation study of oral alpelisib in adult patients with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene	134 patients with advanced solid malignancies Male: 36 Female: 98	Repeated dose 30-450 mg q.d. and 120-200 mg b.i.d. Fed	AUCinf, AUClast, Cmax
Study CBYL719**X1101**	Phase I dose-escalation study of alpelisib in Japanese patients with advanced solid tumours	25 patients with advanced solid tumours Male: 15 Female: 10	Repeated dose 90-400 mg q.d. Fasted and Fed	AUCinf, AUClast, Cmax
Combination PK studies with fulvestrant in subjects with advanced breast cancer				

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
Study CBYL719**X2101**	Phase Ia expansion arm in combination with fulvestrant in HR+, HER2- advanced breast cancer after multiple lines of therapy	87 patients with HR+, HER2- advanced breast cancer Male: 1 Female: 86	Repeated dose 300, 350, 400 mg q.d. Fed	AUCinf, AUClast, Cmax, CL/F, Vz/F
Study CBYL719**C2301** (SOLAR-1)	Phase III randomized double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR+, HER2- advanced breast cancer.	341 patients with HR+, HER2- advanced breast cancer Male: 1 Female: 340	Repeated dose 300 mg q.d. Fed	AUCinf, AUClast, Cmax, CL/F, Vz/F
Studies in subjects with PROS				
CBYL719**F12201** EPIK-P2/ Prospective, Interventional[a]	Phase II double-blind study with an upfront 16- week randomized, placebo-controlled period, in male and female paediatric and adult patients (≥ 2 years of age) with PROS	All patients: 188 patients with PROS **Group 1** (adult [≥ 18 years of age]): 81 Alpelisib: 54 Placebo: 27 **Group 2** (paediatric [6-17 years of age]): 84 Alpelisib: 56 Placebo: 28 **Exploratory Group 4** (paediatric [2-5 years of age]): 7 **Exploratory Group 5** (paediatric [6-17 years of age]): 16 Total patients: 188	**Group 1**: 125 mg / dose escalations permitted beginning Week 29[c] **Group 2**: 50 mg / dose escalations permitted beginning Week 29[d] **Exploratory Group 4**: 50 mg / dose escalations permitted beginning Week 25[d] **Exploratory Group 5:** 125 mg / dose escalations permitted[c]	AUCinf, AUClast, Cmax, CL/F, Vz/F

[a] Only Groups 1, 2, 4 and 5, which are included in the primary analysis Clinical study report (CSR), are discussed in this table.
[b] All doses were FCT administered q.d. p.o., to be taken with food
[c] Fixed-step escalations were from 125 mg to 200 mg and from 200 mg to 250 mg q.d. p.o
[d] Fixed-step escalations were from 50 mg to 125 mg, from 125 mg to 200 mg, and from 200 mg to 250 mg q.d. p.o.
Source:BYL719 PROS SCP-Table 1-1

5.2.1. Methods

Bioanalysis

For the F12101 study, human K3EDTA plasma concentrations of alpelisib samples were measured using the previously validated HPLC-MS/MS method "DMPK R1600667". This method has undergone three additional validation report amendments (DMPK R1600667-04, 05, and 06). Notably, amendment 04 extended long-term stability at −70 °C to 1,635 days, and Amendment 06 provided cross-validation data to support method facility transfer from WUXI (China) to Veeda (India).

In EPIK-P2, plasma alpelisib concentrations were quantified partially at WUXI using the established HPLC-MS/MS "DMPK R1400105" method and primarily at Veeda where the DMPK R1600667 method (as validated by Amendment 06) was applied.

Description and validation reports (DMPK R1600667-04, 05, and 06 and report DMPK R1400105-a/a-01) were submitted demonstrating satisfactory performance across key parameters. The relevant study-specific bioanalytical reports (*report DMPK RCBYL719F12101* for F12101 and *report DMPK RCBYL719F12201a* and interim report *DMPK RCBYL719F12201-int* for EPIK-P2) include method performance monitoring, certificate of analysis and ISR data; all meeting acceptance criteria.

Pharmacokinetic analyses

In studies F12101 and EPIK-P2, plasma PK parameters assessed included Cmax, Ctrough, Tmax, AUCs (AUC0-t, AUC0-24, AUCinf), MRTlast, CL/F, Vz/F, λz, T1/2 in all evaluable participants. Standard non-compartmental (model-independent) methods were applied using Phoenix WinNonlin v8.3 (Pharsight, Mountain View, CA) for PK parameter calculation.

A Population PK analysis (Report cbyl719f1-population-pk, release date 16-Mar-2025) was performed including PK data from adults and paediatric patients with PROS enrolled in EPIK-P2 study. The Pop-PK model was developed using non-linear mixed effects modeling (NLME) implemented in the Monolix software system, Monolix Suite2023R1 (Lixoft, Paris, France). All model building was performed using the Stochastic Approximation Expectation-Maximization (SAEM) method.

PK/PD and Exposure-response analyses

Exposure–response (E-R) and PK/PD analyses were conducted in pediatric and adult PROS patients from the EPIK-P2 study (Population PK/PD and E-R report, 17-Mar-2025). Analyses were performed using SAS 9.4, R 3.4.1, and Monolix Suite2023R1 (Lixoft, Paris, France). The analyses included data up to 25-Sep-2024.

5.2.2. Pharmacokinetics

5.2.2.1. Absorption

Following oral administration of alpelisib, either in film-coated tablets or granules formulation, median time to reach peak plasma concentrations (Tmax) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen.

In patients with PROS (EPIK-P2 Study), following oral administration of alpelisib with food, the median Tmax was 3.0 hours after dosing.

Absolute bioavailability

The absolute bioavailability has not been investigated following a formal PK study. Based on absorption modeling, bioavailability was estimated to be very high (>99%) under fed conditions but lower under fasted conditions (~68.7% at a 300 mg alpelisib dose recommended in the oncology setting).

Relative bioavailability

A PK comparison between the crushed tablet administered as an oral suspension (Test) and the intact tablet (Reference) was conducted in Phase IB of study X2104 in cancer patients (parallel group, single and repeated dose, fed state, 300 mg alpelisib + cetuximab). **Figure 3** shows that the geometric mean plasma concentration–time profiles were similar across formulations on Day 1 and Day 15. Following a single dose (Day 1), AUClast and Cmax for the suspension (n=17) were slightly higher (by 21% and 19%, respectively) than those observed with the intact tablet (n=15). At steady state (Day 15), exposure remained comparable between formulations (AUClast: 26,300 vs. 28,600 ng·h/mL; Cmax: 2,300 vs. 2,600 ng/mL). A post-hoc analysis of combined Day 1 and Day 15 data (**Table 2**) showed GMRs (suspension vs. intact tablet) ranging from 0.96 to 1.00, with all 90% confidence intervals within 0.72–1.39.

Figure 3. Geometric mean plasma concentration-time profiles for BYL719 after a single (C1D1) and multiple (C1D15) oral daily doses of BYL719 for Phase Ib (PK analysis set)

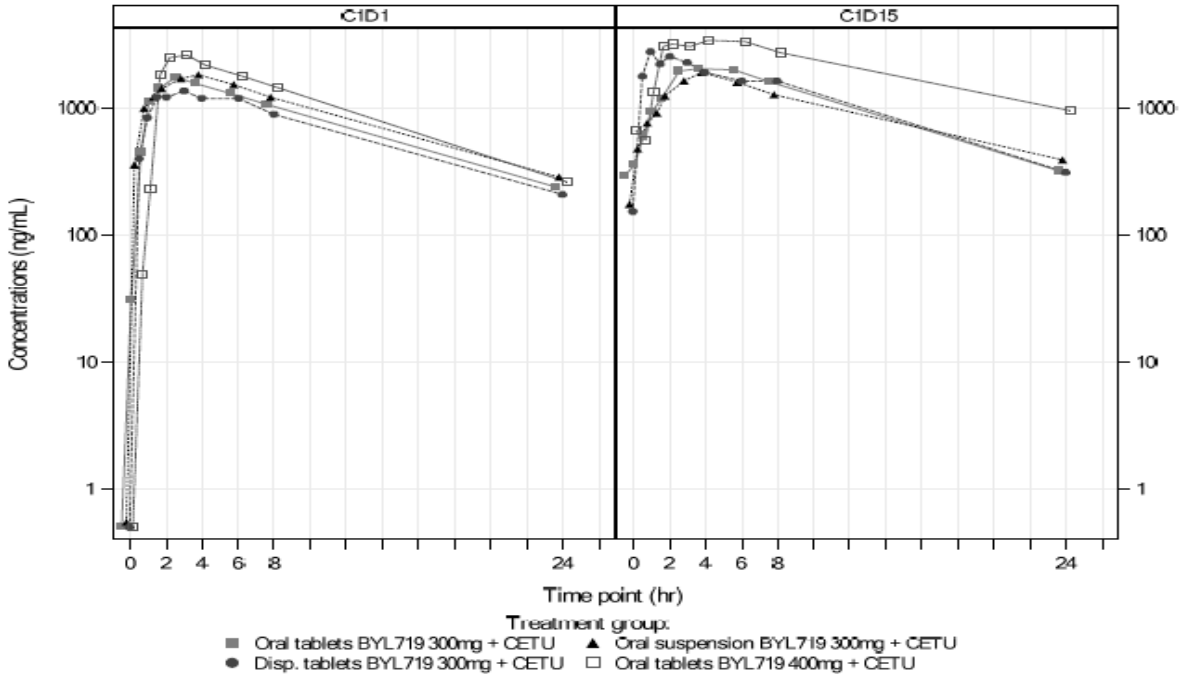


Table 4. Statistical analysis of alpelisib PK after 300 mg oral administration as a crushed FCT suspension or intact FCT

				Crushed FCT suspension / Intact FCT
Parameter	**Treatment**	**N**	**Adjusted geometric mean**	**Geometric mean ratio (90% CI)**
Cmax (ng/mL)	Crushed FCT suspension	16	2202	1.00 (0.72, 1.39)
	Intact FCT	15	2205	
AUC[1] (ng*h/mL)	Crushed FCT suspension	13	26548	

	Intact FCT	12	27675	0.96 (0.77, 1.19)

N: number of patients contributing a PK parameter value
[1] AUC defined as AUCinf for Day 1 and AUC0-24h for Day 15

5.2.2.2. Bioequivalence

Study F12101

This Phase I, single-centre, randomized, open-label, three-period crossover study evaluated the bioequivalence of alpelisib 50 mg granule and tablet formulations in healthy participants under fed conditions. It also assessed the effect of a low-fat, low-calorie (LFLC) meal versus fasting on the PK of alpelisib granules. Each subject received a sequence of three treatments: A (50 mg alpelisib tablet, fed), B (50 mg alpelisib granule, fed), and C (50 mg alpelisib granule, fasted).

The median and arithmetic mean (± SD) plasma concentration–time profiles for FCT (Treatment A) and granules (Treatment B) under fed conditions are shown in **Figure 4**. The corresponding primary PK parameters following a single oral 50 mg dose are summarized in **Table 3**.

Bioequivalence between the two formulations under fed conditions was demonstrated: the 90% confidence intervals (CIs) for the geometric mean ratios (granules vs. tablet) of AUCinf, AUClast and Cmax were all within the pre-defined acceptance range of 0.80–1.25 (**Table 4**).

Figure 4. Study F12101. Median and arithmetic mean (SD) plasma concentration-time profiles for alpelisib.

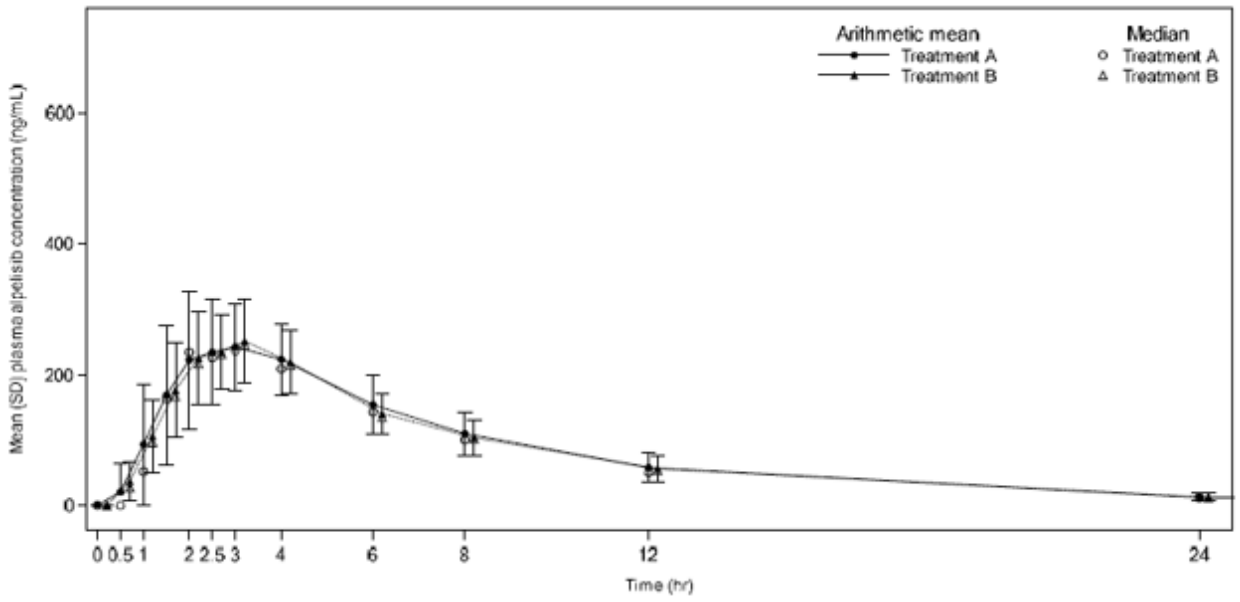


Table 5: Primary PK parameters - Study F12101

Parameter	Statistics	Treatment A	Treatment B
AUCinf (h*ng/mL)	n	48	48
	Mean (SD)	2150 (528)	2110 (483)
	CV%	24.5	22.9
	Geo-mean	2090	2060
	Geo-CV%	24.3	23.7
	Median	2050	2050
	Min-Max	1370-3270	1180-3060
AUClast (h*ng/mL)	n	48	48
	Mean (SD)	2050 (495)	2010 (458)
	CV%	24.1	22.8
	Geo-mean	2000	1950
	Geo-CV%	24.1	23.9
	Median	1980	1960
	Min-Max	1260-3140	1050-2950
Cmax (ng/mL)	n	48	48
	Mean (SD)	284 (69.6)	269 (64.9)
	CV%	24.5	24.1
	Geo-mean	277	262
	Geo-CV%	24.4	24.6
	Median	269	259
	Min-Max	172-526	124-429

Treatment A: Single oral dose of alpelisib FCT at 50 mg under fed state.
Treatment B: Single oral dose of alpelisib granule dosage form at 50 mg under fed state.

Table 6. Study F12101. Bioequiavalnce results between alpelisib 50 mg granules and FCT formulations in the fed state.

					Treatment comparison		
						90% CI	
PK parameter (unit)	Treatment	n	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUCinf (h*ng/mL)	B	48	2060	B / A	0.984	0.952	1.02
	A	48	2090				
AUClast (h*ng/mL)	B	48	1950	B / A	0.980	0.946	1.02
	A	48	1990				
Cmax (ng/mL)	B	48	261	B / A	0.947	0.891	1.01
	A	48	276				
Tmax (h)	B	48	2.51	B - A	0.005	-2.00	3.00
	A	48	2.50				

Treatment A: Single oral dose of alpelisib FCT at 50 mg under fed state (reference).
Treatment B: Single oral dose of alpelisib granule dosage form at 50 mg under fed state (test).
Model is a linear fixed effect model of the log-transformed PK parameters, as described in the statistical methods. The model included treatment (Treatment B as test or Treatment A as reference), sequence, period and subjects nested within sequences as fixed factors.
Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI on the original scale. n = number of observations used for analysis.
For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

The effect of food on the 50 mg granule formulation was evaluated by comparing PK profiles under fed (LFLC meal, Treatment B) and fasted (Treatment C) conditions. As shown in **Figure 5**, the plasma concentration–time profiles were similar. The 90% confidence intervals for geometric mean ratios (fed vs. fasted) of AUCinf, AUClast, and Cmax were all within the 0.80–1.25 bioequivalence range (**Table 5**), indicating no clinically relevant food effect.

Figure 5: Median and arithmetic mean (SD) plasma concentration-time profiles for alpelisib (PAS2): Linear view - Study F12101.

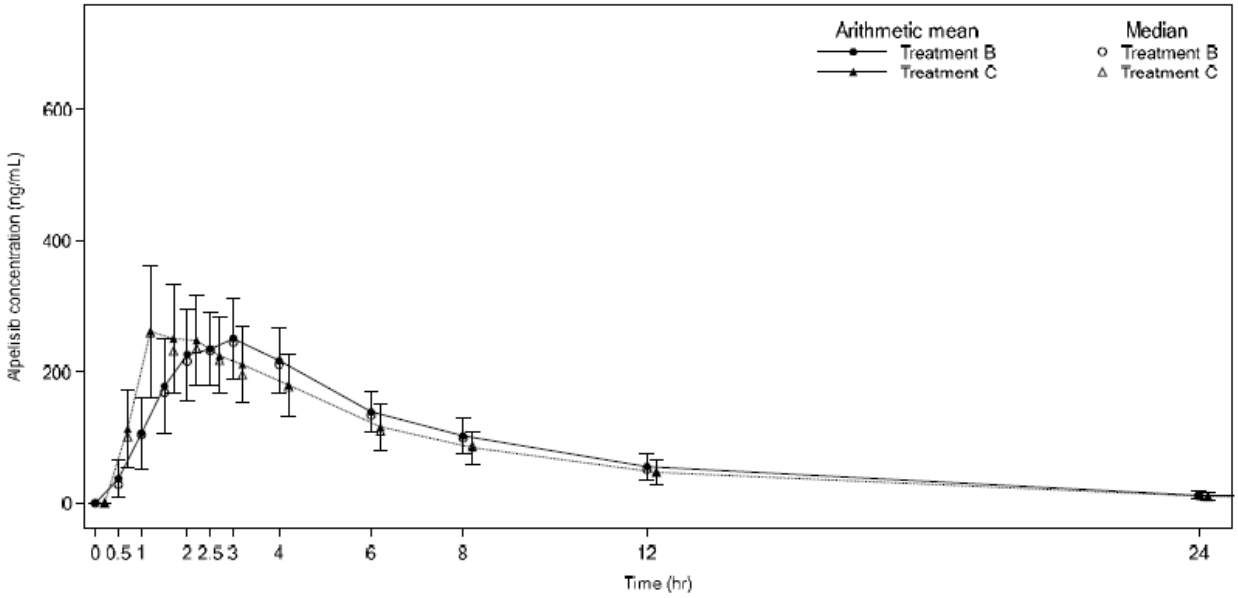


Table 7. Statistical analysis of primary PK parameters for alpelisib granule dosage form in a fed vs fasted state.

					Treatment comparison		
						90% CI	
PK parameter (unit)	**Treatment**	**n**	**Adjusted geo-mean**	**Comparisons**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf (h*ng/mL)	B	50	2040	B / C	1.07	1.03	1.11
	C	54	1910				
AUClast (h*ng/mL)	B	50	1940	B / C	1.07	1.02	1.12
	C	54	1810				
Cmax (ng/mL)	B	50	260	B / C	0.938	0.881	0.999
	C	54	277				
Tmax (h)	B	50	2.51	B - C	1.47	-0.493	3.02
	C	54	1.01				

Treatment B: Single oral dose of alpelisib granule dosage form at 50 mg under fed state (test).
Treatment C: Single oral dose of alpelisib granule dosage form at 50 mg under fasted state (reference).
Model is a linear mixed effect model of the log-transformed PK parameters, as described in the statistical methods. The model included treatment (Treatment C as reference or Treatment B as test), sequence and period as fixed factors and subject nested within sequence as a random factor.
Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n = number of observations used for analysis.
For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

5.2.2.3. Distribution

The newly estimated steady state Vss/F of 136 L in the PROS population (using the Pop-PK approach) is consistent with the previously known value of 114 L (CV 49%) in oncology patients, indicating a wide distribution of alpelisib into tissues.

5.2.2.4. Metabolism

No additional data on elimination and metabolism of alpelisib were provided or requested.

In vitro studies demonstrated that formation of the hydrolysis metabolite BZG791 by chemical and enzymatic amide hydrolysis was a major metabolic pathway, followed by CYP3A4-mediated hydroxylation. Alpelisib hydrolysis occurs systemically by both chemical decomposition and enzymatic hydrolysis via ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) not limited to the liver. CYP3A4-mediated metabolites and glucuronides amounted to ~15% of the dose; BZG791 accounted for ~40-45% of the dose. The rest of the dose, which was found as unchanged alpelisib in urine and faeces, was either excreted as alpelisib or not absorbed.

5.2.2.5. Elimination

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

The Pop-PK estimates for CL/F (12.3 L/h) and T1/2 (7.7 h) in a typical PROS patient were consistent with previously reported values.

5.2.2.6. Dose proportionality and time dependency

No new data regarding PK linearity demonstrated within the dose range 30 to 450 mg under fed state are provided.

Following multiple once-daily doses in patients with PROS, steady-state exposure (AUCss) of alpelisib was slightly higher than single-dose exposure (AUCinf), indicating minimal accumulation. In adults receiving 125 mg, the mean AUCss was 9460 ng·h/mL compared to 7590 ng·h/mL after a single dose, corresponding to an accumulation ratio of 1.24. In pediatric patients aged 6 <18 years receiving 50 mg, mean AUCss and AUCinf were 5010 ng·h/mL and 5120 ng·h/mL, respectively, resulting in an accumulation ratio of 1.02.

5.2.2.7. Pharmacokinetics in the target population

EPIK-P2 Study

This is an ongoing Phase II, multicentre study with an upfront 16-week, randomized, double-blind, placebo-controlled period for Groups 1 and 2, and subsequent extension periods to assess the efficacy, safety and PK of alpelisib in pediatric and adult patients with PROS. After 16 weeks the patients randomized to placebo in Groups 1 and 2 were switched to treatment with the alpelisib tablet dosage form (end of the double-blind period at week 24). Exploratory Groups 4 and 5 were designed as open-label and exploratory in nature. All alpelisib doses are to be administered with food.

At the time of the current submitted primary analysis (cut-off date 20-Mar-2024), the study has enrolled adult and pediatric patients across groups 1, 2, 4 and 5. Step-wise dose escalation as needed for response optimization was permitted for patients aged 6 years and older in the extension period as illustrated in **Figure 6** and **Table 6**.

Figure 6: EPIK-P2 study design

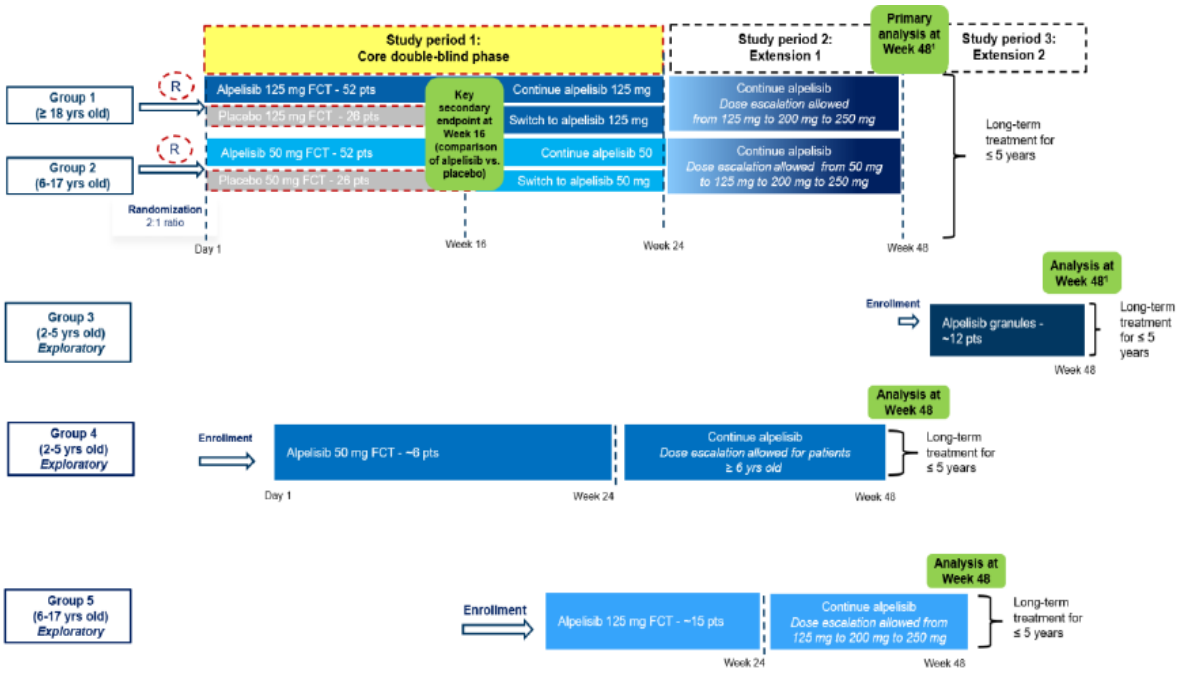


Table 8. EPIK-P2 study: dose, age groups and PK sampling details

Study Group	Data available for inclusion in MAA?	Age	Starting Dose (q.d., orally with food) & Formulation	Intrapatient Dose Escalation	PK Sampling
Group 1	Yes	≥ 18 years	125 mg alpelisib FCT or matching placebo*	Stepwise dose escalation for response optimization allowed beginning at Week 29	Full PK on Week 17, Day 1. Predose and 3 h sampling on Day 1 of Weeks 20, 28 and ≥4 weeks after each escalation.
Group 2	Yes	6 to 17 years	50 mg alpelisib FCT or matching placebo*		
Group 3	No	2 to 5 years	Age-based dosing	Escalation not permitted until patient reaches 6 years and Week 25	3 h sample on Week 1, Day 1. Predose and 3 h sampling Week 4 Day 1.
Group 4	Yes	2 to 5 years	50 mg alpelisib FCT		
Group 5	Yes	6 to 17 years	125 mg alpelisib FCT	Stepwise dose escalation for response optimization allowed beginning at Week 25	Full PK on Week 1, Day 1. Predose and 3 h sample on Week 4, Day 7.

*After 16 weeks, patients randomized to placebo were switched to alpelisib

PK results

The plasma PK profile of alpelisib over the daily dosing interval at the starting dose during the core treatment period of EPIK-P2 is shown as group averages in **Figure 7**. This includes patients in Group 1 (adults receiving 125 mg), Group 2 (paediatric patients aged 6 <18 receiving 50 mg), and Group 5 (paediatric patients aged 6 <18 receiving 125 mg). For placebo-randomized patients, the profile reflects the first dose; for alpelisib-randomized patients, it represents steady-state PK.

Alpelisib PK parameters following single and repeated dosing are summarized in **Table 7** for adults (Group 1) and paediatric patients aged 6–<18 (Groups 2 and 5) with PROS. Alpelisib concentrations declined with an apparent mono-exponential half-life of 6 hours. Inter-individual variability (IIV) was moderate to high, with steady-state AUC0-24h coefficients of variation (CV%) of 43.6% in adults and 43.8% in paediatric patients.

Average alpelisib concentrations at steady state (≥4 weeks after dose escalation), measured pre-dose and 3 hours post-dose (C3h), are shown in **Figure 8**. Corresponding steady-state trough and C3h concentrations in adult and pediatric PROS patients are summarized in **Table 8**.

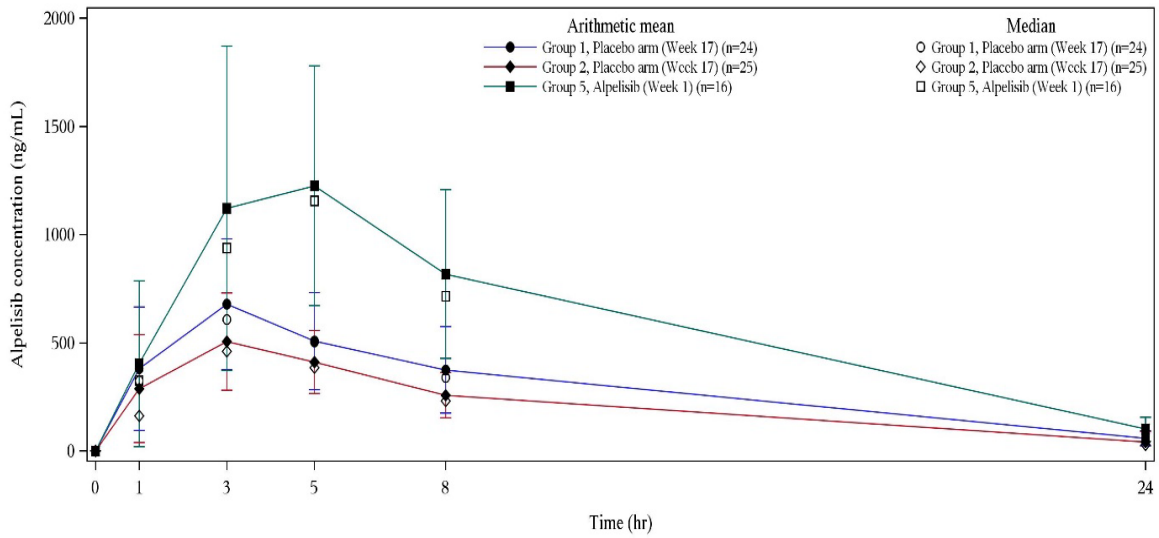
In adults, key parameters at the 125 mg dose included a mean Cmax of 726 ng/mL (single dose), 913 ng/mL (steady state), and a steady-state AUC0-24h of 9460 ng·h/mL. At the target 250 mg dose (n = 17), steady state mean Cmax was 1840 ng/mL and Ctrough was 195 ng/mL.

In pediatric patients aged 6 to <18 years, key parameters at the 50 mg dose included a mean single-dose Cmax of 537 ng/mL and steady-state AUC0-24h of 5120 ng·h/mL. At steady state, for the 125 mg dose, mean C3h was 1250 ng/mL and Ctrough was 143 ng/mL.

In younger children aged 2 to <6 years (n = 6) following 50 mg dosing, mean steady state C3h and Ctrough values were 931 ng/mL and 127 ng/mL, respectively.

Figure 7. Arithmetic mean (SD) alpelisib plasma concentration-time profiles in EPIK-P2 Groups 1 and 2 at Week 17 Day 1 and Group 5 at Week 1 Day 1.

First dose PK profiles



*Subjects in Groups 1, 2 and 5 were randomized to receive alpelisib treatments of 125 mg q.d., 50 mg q.d. and 125 mg q.d., respectively, in the core treatment period displayed in this figure.
**PK profile corresponds to first dose of alpelisib for patients randomized to placebo arm in Groups 1 and 2 as well as patients enrolled in Group 5 and to PK steady state for patients randomized to alpelisib arm in Groups 1 and 2.

Steady-state PK profiles

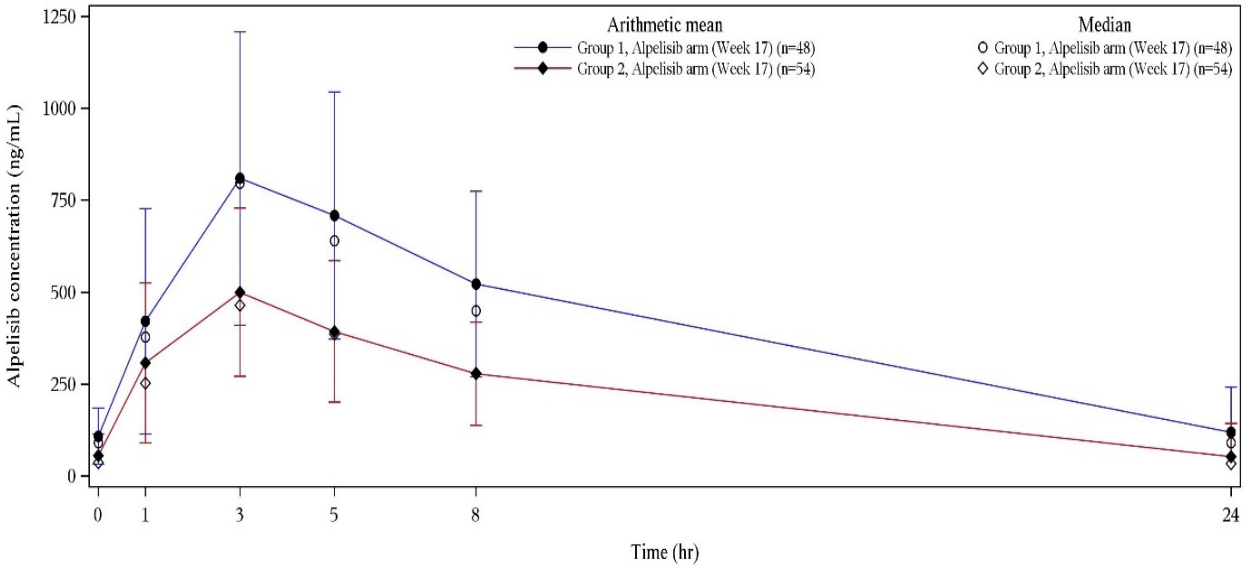
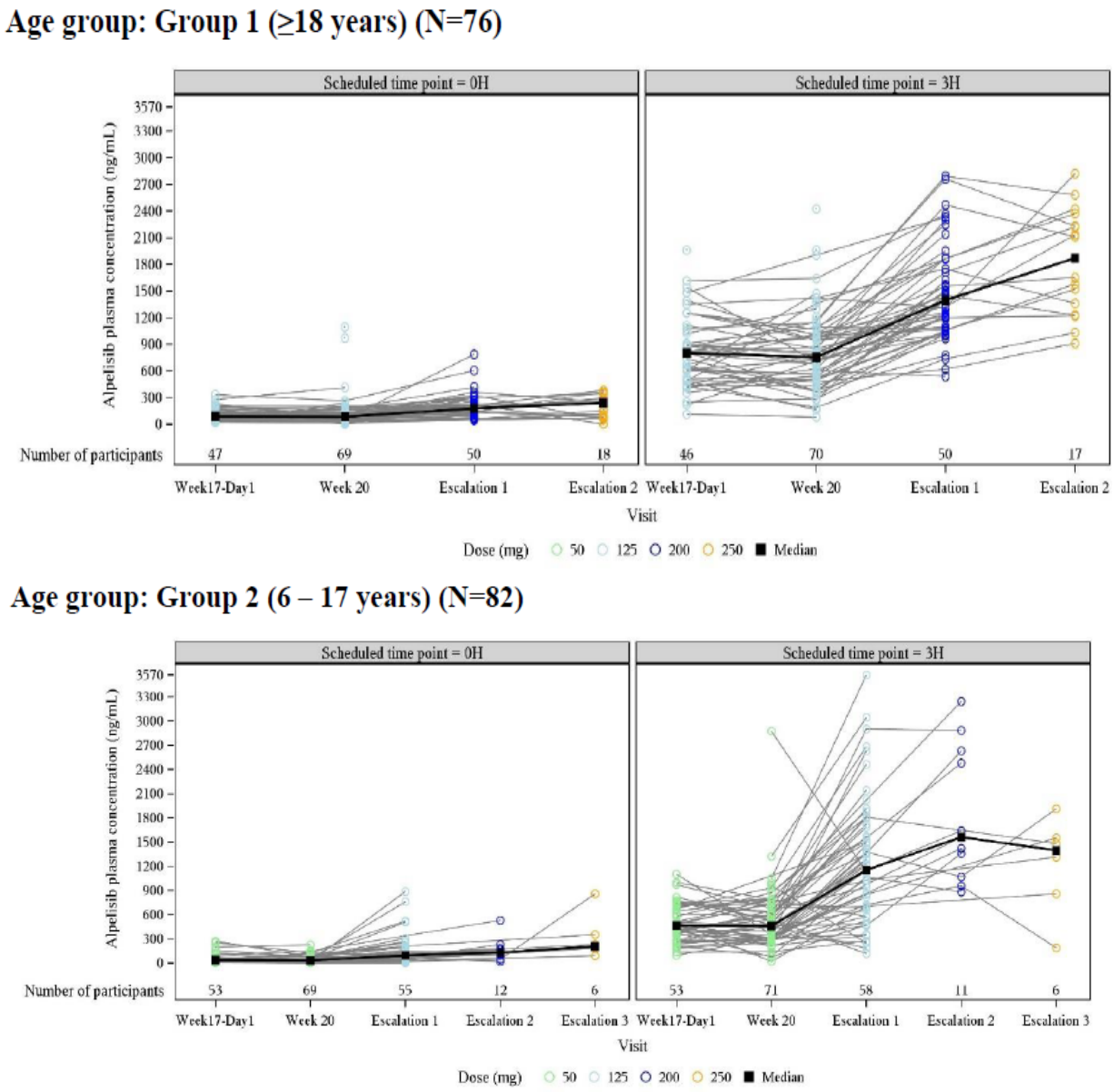


Table 9. Alpelisib plasma PK parameters for adult and pediatric patients with PROS after single or repeated dosing (EPIK-P2)

		Cmin *(ng/mL)*	**Cmax** *(ng/mL)*	**Tmax** *(h)*	**AUCinf** *(ng*h/mL)*	**AUC0-24h,ss** *(ng*h/mL)*	**T1/2** *(h)*
Group 1 (≥18 y)	*single 125 mg dose*	NA	n=24; 726 (294, 40.6%)	n=24; 2.65 (1.00, 5.03)	n= 21; 7590 (3100, 40.8%)	-	n=21; 6.13 (4.69, 7.45)
	repeated 125 mg dose	n=48; 95.5 (62.8, 65.7%)	n=48; 913 (362, 39.6%)	n=48; 3.15 (0.667, 7.58)	-	n=40; 9460 (4130, 43.6%)	n=31; 6.31 (4.64, 9.92)
Group 2 (6-17 y)	*single 50 mg dose*	NA	n=24; 537 (184, 34.3%)	n=24; 2.87 (0.867, 5.50)	n= 20; 5010 (1480, 29.6%)	-	n=20; 5.12 (4.25, 9.02)
	repeated 50 mg dose	n=53; 41.6 (40.8, 98.0%)	n=53; 541 (236, 43.6%)	n=53; 2.87 (0.867, 5.08)	-	n=45; 5120 (2240, 43.8%)	n=38; 5.54 (4.06, 9.08)
Exploratory Group 5 (6-17 y)	*single 125 mg dose*	NA	n=16; 1410 (582, 41.4%)	n=16; 3.73 (0.967, 8.02)	n=8; 16000 (8260, 51.5%)	-	n=8; 5.58 (3.63, 7.56)

Figure 8. Individual alpelisib plasma pre-dose and 3-hour concentrations in EPIK-P2 at PK steady-state with median by visit and dose in Groups 1 and 2.



Only includes PK steady-state concentrations, i.e. Week 17 Day 1 concentrations from patients randomized to placebo and switching to alpelisib at Week 17 Day 1 are not included in this figure

Table 10. Alpelisib dose-ranging steady-state trough (pre-dose) and 3-hour (C3h) post-dose plasma concentrations from adult and pediatric patients with PROS (EPIK-P2 PAS)

	Dose *(q.d.)*	Ctrough *(ng/mL)*	C3h *(ng/mL)*
Group 1	*125 mg**	n=47; 104 (70.8, 67.9%)	n=46; 817 (400, 48.9%)
	*200 mg***	n=50; 201 (134, 66.7%)	n=50; 1480 (529, 35.7%)
	*250 mg***	n=18; 195 (117, 60.2%)	n=17; 1840 (576, 31.3%)
Group 2	*50 mg**	n=53; 55.3 (59.0, 106.6%)	n=53; 500 (229, 45.8%)
	*125 mg***	n=55; 143 (170, 118.9%)	n=58; 1250 (765, 61.1%)
	*200 mg***	n=12; 158 (129, 82.1%)	n=11; 1830 (830, 45.4%)
	*250 mg***	n=6; 317 (278, 87.8%)	n=6, 1220 (610, 50.1%)
Exploratory Group 4	*50 mg****	n=6; 127 (107, 84.5%)	n=6; 931 (642, 69.0%)
Exploratory Group 5	*125 mg****	n=16; 108 (67.3, 62.6%)	n=15; 1320 (674, 51.0%)

Values are mean (standard deviation, CV%)
n = number of patients with non-missing values
*Measured at Week 17 from patients randomized to alpelisib treatment. (Groups 1 and 2, Core Period, Week 17)
** Measured from all adults (Group 1) or all Group 2 pediatric patients in the extension period at least 4 weeks after individualized dose escalation. (Groups 1 and 2, Extension Period)
***Measured at Week 4 from patients enrolled in Group 4 or Group 5. (Groups 4 and 5)

5.2.2.8. Population Pharmacokinetics

In the new Pop-PK analysis, the PK data in breast cancer patients - from Phase I studies X1101 and X2101 (intensive sampling) and Phase III study C2301 (sparse sampling but large patient population) - was supplemented with PK data from the confirmatory EPIK-P2 study in adult and pediatric patients with PROS, based on the interim database lock for the primary analysis (20-Mar-2024).

The analysis included 10,028 alpelisib concentrations and 159,422 dosing events from 697 patients, including 181 (26%) from the EPIK-P2 study (7 aged 2–<6 years, 98 aged 6–<18 years, 76 adults), contributing 1,554 concentrations (15.5%). Of all concentrations, 226 (2%) were BLQ; in EPIK-P2, 17 (1%) were BLQ, none from the 2–<6 years group.

The final Pop-PK model consisted of a one compartment model with zero-order absorption (duration Tk0), absorption lag-time and linear elimination. IIV was estimated on all parameters (Tk0, Tlag, V/F and CL/F). RUV was modelled using a combined (additive and proportional) error. The significant covariates impacting PK of alpelisib were: fulvestrant intake and BW on V/F and gender, BW, patient population, and renal impairment on CL/F.

Table 9 provides the PK parameter estimates of the final Pop-PK model of alpelisib.

Goodness-of-fit diagnostic plots for the final Pop-PK model are presented in **Figure 9**, **Figure 10**, **Figure 11** and **Figure 12**. Prediction-corrected visual predictive checks (pcVPC) are shown in **Figure 13**.

Compared to reference cancer patients (CL = 10.3 L/h), the effect of indication led to an increase of approximately 19.4% in CL/F. Accordingly, for a given dose, the steady-state 24-hour AUC is expected to be 16.2% lower in PROS patients than in cancer patients of same gender, BW, and with same renal function. The CL/F in male PROS patients is predicted to be 20.8% higher compared to the CL/F in female PROS patients with same BW and renal function. The effects of significant covariates on alpelisib exposure based on the final model are summarised in **Table 10**.

Table 11: Parameter estimates of the Final Aleplisib Pop-PK model

Parameter	Estimate	RSE (%)	Solar-1 estimates
Fixed effects			
$Tlag$ (h)	0.375	4.72	0.43
$Tk0$ (h^{-1})	1.20	4.01	
V/F (L)	136	2.5	113.88[&]
Cl/F (L/h)	10.3	1.96	9.18[&]
Covariate effect *on* V/F			
$Fulvestrant\ effect^{@}$	0.194	20.6	
$Weight\ effect^{\#}$	0.759	7.13	0.52
Covariate effect *on* Cl/F			
$Gender\ effect\ (male)$	0.189	20	
$Weight\ effect^{\#}$	0.551	8.19	0.63
$Poptype\ effect\ (PROS)$	0.177	21.9	
$Renal\ impairment\ effect^{\$}$	-0.267	20	
Standard deviation of the random effects			
$Tlag$	0.726	5.84	
$Tk0$	0.636	5.42	
V/F	0.414	3.94	
Cl/F	0.341	3.16	
Residual error			
Additive component	6.71	6.83	
Proportional component	0.424	0.896	

@: versus no treatment with Fulvestrant.
#: Relative to the reference weight (61.2 kg).
$: Effect of moderate/severe renal impairment versus mild/normal renal function.
&: In SOLAR-1, and the reference weight is 67 kg.
In SOLAR-1, the estimate of the first-order absorption parameter ka=0.75 h^{-1}.
*The standard deviation (SD) of the between-subject random effect on log-transformed apparent clearance (0.341) corresponds to a CV of 35.1%, calculated as 100 x sqrt(exp(SD^2) – 1). (Table 11-4). The CV of the apparent volume similarly calculated is 43.3%.
Source: <root>/runs/popPK_SolarPHI_EPIK/Final_covmodel_base_expert.mlxtran

Figure 9: Goodness-of-fit plots for the final Pop-PK model: Observed Versus IPRED

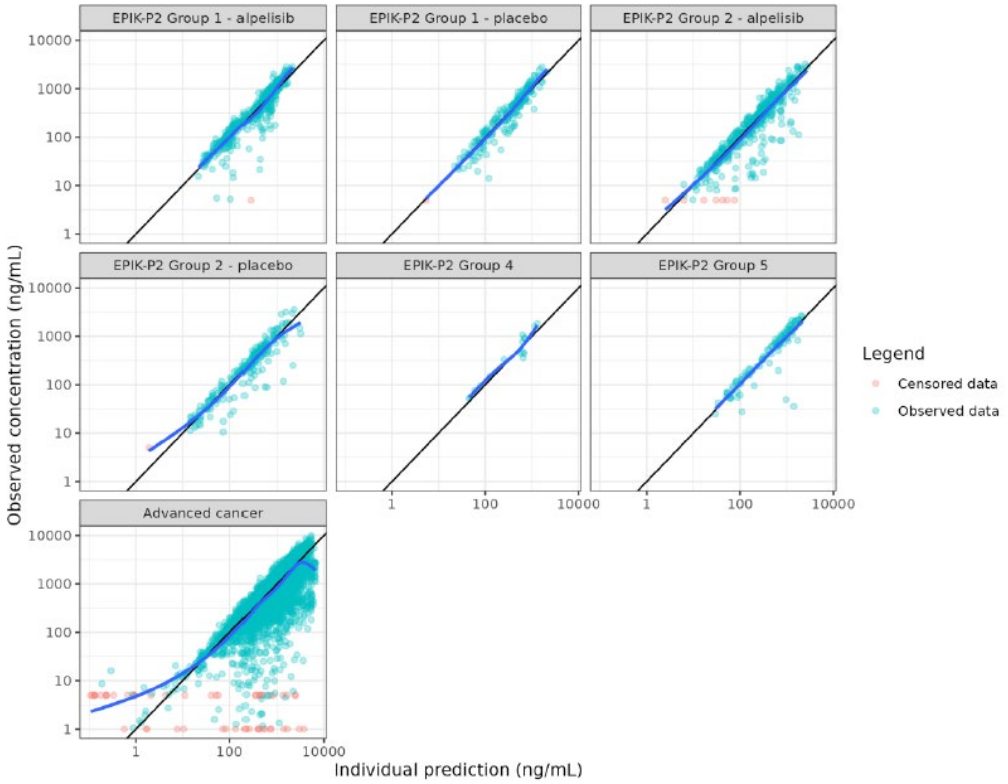


Figure 10: Goodness-of-fit plots for the final Pop-PK model: NPDE Versus time

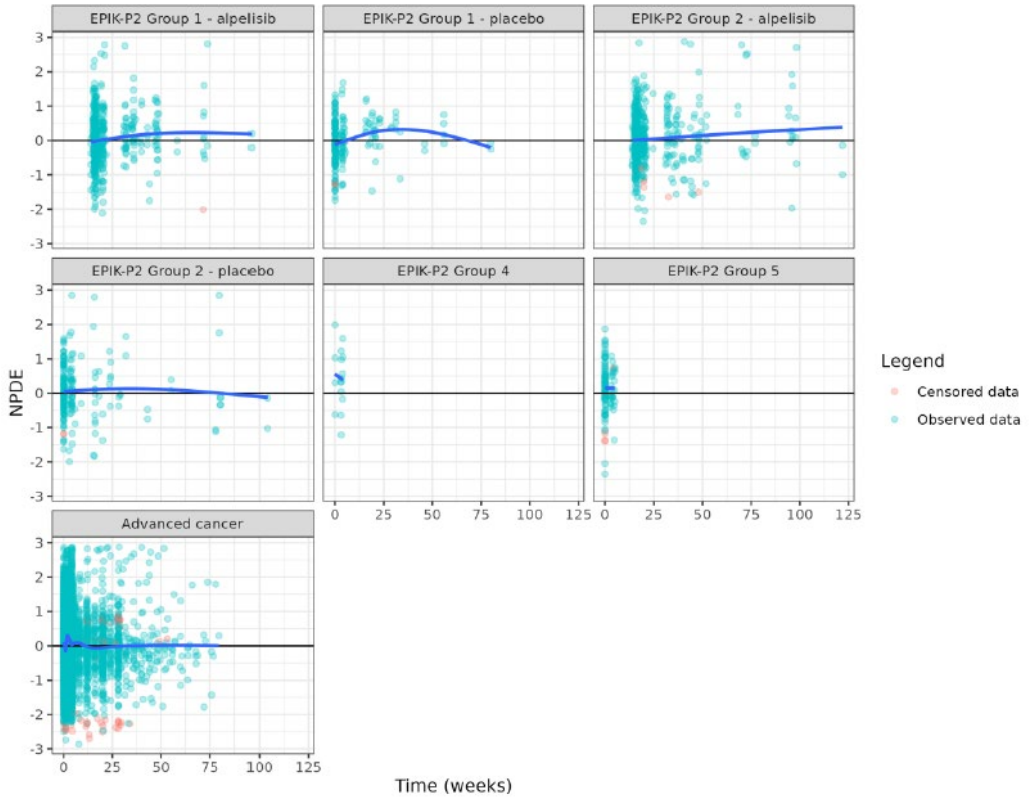


Figure 11: Goodness-of-fit plots for the final Pop-PK model: IWRES Versus IPRED

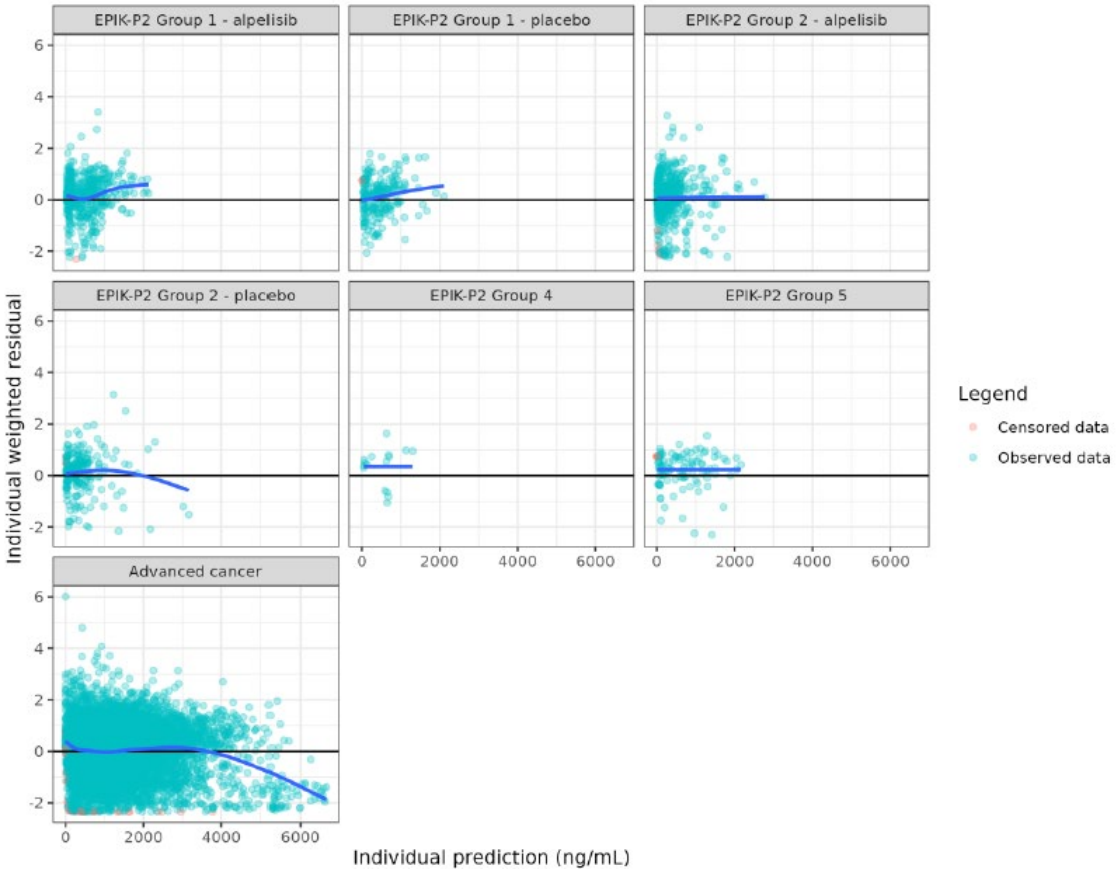


Figure 12: Goodness-of-fit plots for the final Pop-PK model: IWRES Versus Time

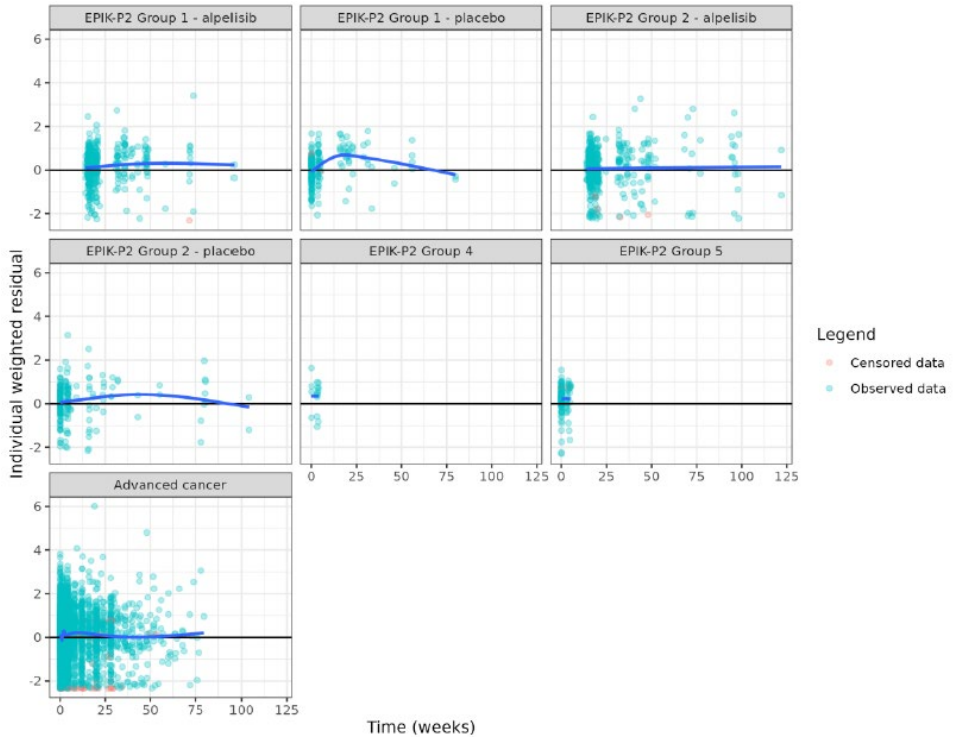


Figure 13: Prediction-Corrected Visual Predictive Checks for the Final Population Model of Paltusotine, to 24 hours.

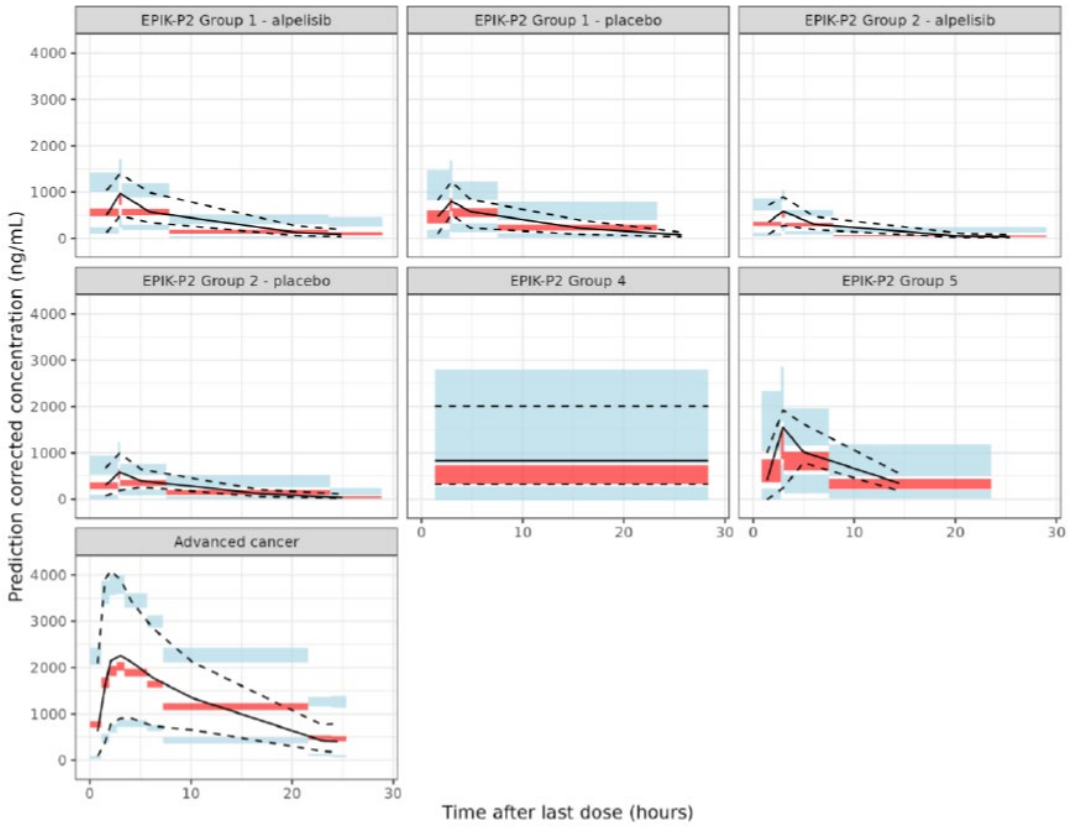


Table 12: Covariate effects of alpelisib on AUC based on the final model

Estimand	Estimate
CL/F of Female 56 kg PROS patient with normal renal function and not under fulvestrant	11.7 L/h
V/F of Female 56 kg PROS patient with normal renal function and not under fulvestrant	127 L
Half-Life of Female 56 kg PROS patient with normal renal function and not under fulvestrant	7.56 h
CL/F of Female 61.2 kg PROS patient with normal renal function and not under fulvestrant	12.3 L/h
V/F of Female 61.2 PROS patient with normal renal function and not under fulvestrant	136 L
Half-Life of Female 61.2 kg PROS patient with normal renal function and not under fulvestrant	7.7 h
CL/F increase in PROS patients versus Cancer patients	19.3 %
AUCss increase in PROS patients versus Cancer patients	-16.2 %
CL/F increase in Male patients versus Female patients	20.8 %
AUCss increase in Male patients versus Female patients	-17.2 %
CL/F increase in 99 kg patients versus 74 kg patients	17.4 %
AUCss increase in 99 kg patients versus 74 kg patients	-14.8 %
CL/F increase in 51 kg patients versus 74 kg patients	-18.5 %
AUCss increase in 51 kg patients versus 74 kg patients	22.7 %
CL/F increase in 63 kg patients versus 37 kg patients	34 %
AUCss increase in 63 kg patients versus 37 kg patients	-25.4 %
CL/F increase in 21 kg patients versus 37 kg patients	-26.8 %
AUCss increase in 21 kg patients versus 37 kg patients	36.6 %
CV of CL/F	35.1 %
CV of V/F	43.3 %

Derivation using the estimated of the Final popPK model reported in Table 7-7.

The 10th percentile, median, and 90th percentile body weight of adult PROS subjects included in the popPK analysis are 51, 74, and 99 kg respectively. Corresponding percentiles are 21, 37, and 63 kg for pediatric PROS subjects.

5.2.2.9. Special populations

Impaired renal function

Results from the mass balance study indicated that excretion in the urine is minor (13.5%) with unchanged alpelisib accounting only for approximately 2%. No dedicated study was conducted to assess the impact of renal impairment on alpelisib PK.

The effect of renal impairment, as assessed by creatinine clearance (CLcr), was evaluated in the Pop-PK analysis, which included subjects with normal (62.1%), mild (28.4%), and moderate (9.5%) renal function. No subjects with severe renal impairment were included, and no clinical experience is available in this population. Moderate renal impairment was retained as a statistically significant covariate on alpelisib CL/F in the final model. The Applicant concluded that mild and moderate renal impairment have no clinically relevant impact on systemic exposure to alpelisib.

Impaired hepatic function

A PK study in healthy adult volunteers and cancer patients with hepatic impairment indicated that moderate and severe hepatic impairment had no clinically meaningful impact on alpelisib exposure. In patients with severe hepatic impairment, mean exposure to alpelisib was increased by approximately 1.26-fold (GMR: 1.00 for Cmax; 1.26 for AUClast; 1.25 for AUCinf).

Gender

The influence of gender on alpelisib PK was evaluated using the Pop-PK approach, with a higher proportion of females (80%) compared to males (20%) in the analysis. Gender was retained as a significant covariate on alpelisib CL/F in the final model, with male PROS patients showing a 20.8% higher CL/F compared to female PROS patients of the same body weight and renal function. This resulted

in a 17.2% lower steady-state exposure AUCss in males compared to females. No dose adjustment based on gender is recommended.

Race / ethnicity

The effect of race on alpelisib PK was evaluated using the Pop-PK approach, with the majority of patients being White (77.8%), followed by Asian (15.3%), Black or African American (0.02%), and other or unknown (0.05%). Race was not retained as a statistically significant covariate in the final model, indicating no clinically relevant impact on systemic exposure to alpelisib. No dose adjustment based on race/ethnicity is recommended.

Weight

No formal investigations were conducted to assess the effect of BW on alpelisib PK. Besides, the effect of BW was evaluated as part of the Pop-PK analysis. The analysis included a wide BW range (10.5–181 kg) with a median BW of 65 kg. Body weight was retained as a statistically significant covariate on both CL/F and V/F, with estimated exponents of 0.551 and 0.759, respectively, indicating that clearance of alpelisib increases with increasing BW. In adults, higher BW (99 kg) is predicted to result in 17.4% higher CL/F and 15% lower steady-state exposure, while lower BW (51 kg) results in 18.5% lower CL/F and 23% higher exposure. In children, BW differences lead to up to 37% increased exposure in lighter patients (21 kg) and 25% lower exposure in heavier patients (63 kg).

Elderly

No patients aged ≥ 65 years with PROS were enrolled in the EPIK-P2 study, and no specific PK data are available for this population. However, based on the Pop-PK analysis including 174 cancer patients aged ≥65 years (approximately 25% of the population), no clinically relevant effect of age on alpelisib systemic exposure in adults was found. The maximum age of included patients was 87 years. Therefore, no significant impact of age on alpelisib PK is predicted for the elderly population. No dose adjustment of alpelisib is recommended for elderly patients.

Paediatric population

In the confirmatory EPIK-P2 study, PK data of alpelisib were obtained from 98 paediatric patients aged 6 to <18 years receiving the recommended dosing regimen starting at 50 mg with dose escalation to 125 mg (and up to 250 mg), and from a limited number of younger children (n = 6) aged 2 to <6 years who received the recommended 50 mg dose.

In the 6 to <18 years group, key exposure parameters at the 50 mg dose included a mean single-dose Cmax of 537 ng/mL and a steady-state AUC0-24h of 5120 ng·h/mL. At the 125 mg dose, mean steady-state C3h and Ctrough were 1250 ng/mL and 143 ng/mL, respectively.
In children aged 2 to <6 years, mean C3h and Ctrough values at steady state following 50 mg dosing were 931 ng/mL and 127 ng/mL, respectively.

5.2.2.10. Pharmacokinetic interaction studies

5.2.2.10.1. PK drug-drug interactions

The drug-drug interaction profile of alpelisib has been thoroughly developed and discussed as part of the marketing authorization process for the breast cancer indication. Since the recommended doses for th PROS indication are lower (50 mg up to 250 mg daily) than those recommended in breast cancer

indications (300mg daily), the DDI profile in this indication can be extrapolated to PROS indication. Hence:

- Impact of other drugs on alpelisib pharmacokinetics:

The effect of different enzymatic inhibitors or inducers and the co-administration of fulvestrant was assessed. The results suggest minor changes of alpelisib concentrations when co-administered with other drugs. CYP3A4 is the predominant enzyme involved in the metabolism of alpelisib, however the overall contribution of CYP3A metabolism was considered low with an estimated fm of 12% (Piqray EPAR,). However, as a post-marketing measure, a DDI study BYL719A2110, on the combination of alpelisib with rifampicin, a strong CYP3A inducer, was assessed in healthy volunteers (EMEA/H/C/004804/II/0012). The results finally demonstrated that a concurrent use of strong CYP3A4 inducers markedly reduced alpelisib exposure (about 74% after multiple doses of alpelisib), and thus may limit the clinical efficacy of alpelisib. Hence, the co-administration of strong CYP3A4 inducers with alpelisib should be avoided (see SmPC).

- Impact of alpelisib on other drugs pharmacokinetics:

In vitro studies indicated that alpelisib may induce CYP2B6, CYP2C9 and CYP3A, and may inhibit CYP2C8, CYP2C9, CYP2C19, and that alpelisib is a time-dependent inhibitor of CYP3A4. The results from the drug-drug interaction study in which alpelisib was co administered with everolimus, a sensitive CYP3A4 substrate, confirmed that there are no clinically significant pharmacokinetic interactions (increase in AUC by 11.2%) between alpelisib and CYP3A4 substrates. No change in everolimus exposure was observed at alpelisib doses ranging from 250 to 300 mg. No dose adjustment is required when co-administering Piqray with CYP3A4 substrates (e.g. everolimus, midazolam) (Piqray EPAR). Additionally, sections 4.5 and 5.2 of the SmPC were updated in order to add drug-drug interaction information based on the final results from the study BYL719A2111. This was a phase 1, open-label, fixed-sequence, two-period drug-drug interaction (DDI) study evaluating the pharmacokinetics of probe substrates for CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 when administered either alone or in combination with repeated doses of alpelisib.

- Impact on intestinal and liver transporters

In vitro interaction studies showed that pharmacokinetic interactions driven by alpelisib inhibition of P-gp, BCRP and OAT3 are expected in patients. The risk of interactions with P-gp, BCRP and OAT3 transporters are adequately described in sections 4.5 and 5.2 of the SmPC.

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

- Acid-reducing agents

The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a low-fat low-calorie (LFLC) meal, AUC_{inf} was decreased on average by 21% and C_{max} by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUC_{inf} and a 51% decrease in C_{max} with ranitidine compared to the fasted state without co-administration of ranitidine. Population pharmacokinetic analysis showed no significant effect of co-administration of acid-reducing agents, including proton pump inhibitors, H2 receptor antagonists and antacids, on the pharmacokinetics of alpelisib. It is agreed that the clinical impact of ranitidine on alpelisib pharmacokinetics might be of minor relevance (around 20% change in AUC and C_{max}) as long as alpelisib is taken immediately after food. Therefore, alpelisib can be co-administered with acid-reducing agents, provided alpelisib is taken immediately after food (see SmPC sections 4.2 and 4.5).

No clinical studies were conducted assessing the drug-drug interaction potential between alpelisib and hormonal contraceptives. However, since alpelisib is a teratogen agent, the absence of a dedicated clinical interaction study with contraceptives warranted a warning in section 4.6 of the SmPC for the lack of data, and a recommendation for women using systemic contraceptive steroids to add a barrier method (sections 4.4, 4.5 and 4.6 of the SmPC and related sections in the PL).

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Alpelisib (BYL719) is an α specific class I PI3K inhibitor belonging to the 2aminothiazole class of compounds. In vitro, alpelisib treatment can potently inhibit the phosphorylation of PI3K downstream targets Akt as well as its various downstream effectors including p-GSK3 beta (S9P), p70S6K (T389) in breast cancer cells. Moreover, alpelisib showed markedly selective efficacy in PIK3CA mutant cell lines when compared to wild-type cell lines and when compared to pan-PI3K inhibitors.

Venot et al (2018) developed and described a mouse model of PROS which partially recapitulates human disease. The alpelisib inhibition of the PI3K/AKT/mTOR pathway resulted in the prevention of the onset of PROS lesions in mice, while withdrawal of alpelisib resulted in recurrence of these lesions. This suggests that continuous administration of alpelisib can relieve PROS symptoms by inhibiting hyperactive PIK3CA signaling.

5.2.3.2. Primary and secondary pharmacology

In vitro, alpelisib treatment can potently inhibit the phosphorylation of PI3K downstream targets Akt as well as its various downstream effectors including p-GSK3 beta (S9P), p70S6K (T389) in breast cancer cells. Moreover, alpelisib showed markedly selective efficacy in PIK3CA mutant cell lines when compared to wild-type cell lines and when compared to pan-PI3K inhibitors.

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The ability of alpelisib to prolong QTc was thoroughly studied in the frame of the MAA for alpelisib in breast cancer treatment. The exposure-QTc analysis did not show any QTc prolongation along the expected alpelisib exposure range.

Besides, the assessment of the PSURs for PIQRAY has not revealed any signal of cardiac arrhythmias-related to adverse events.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

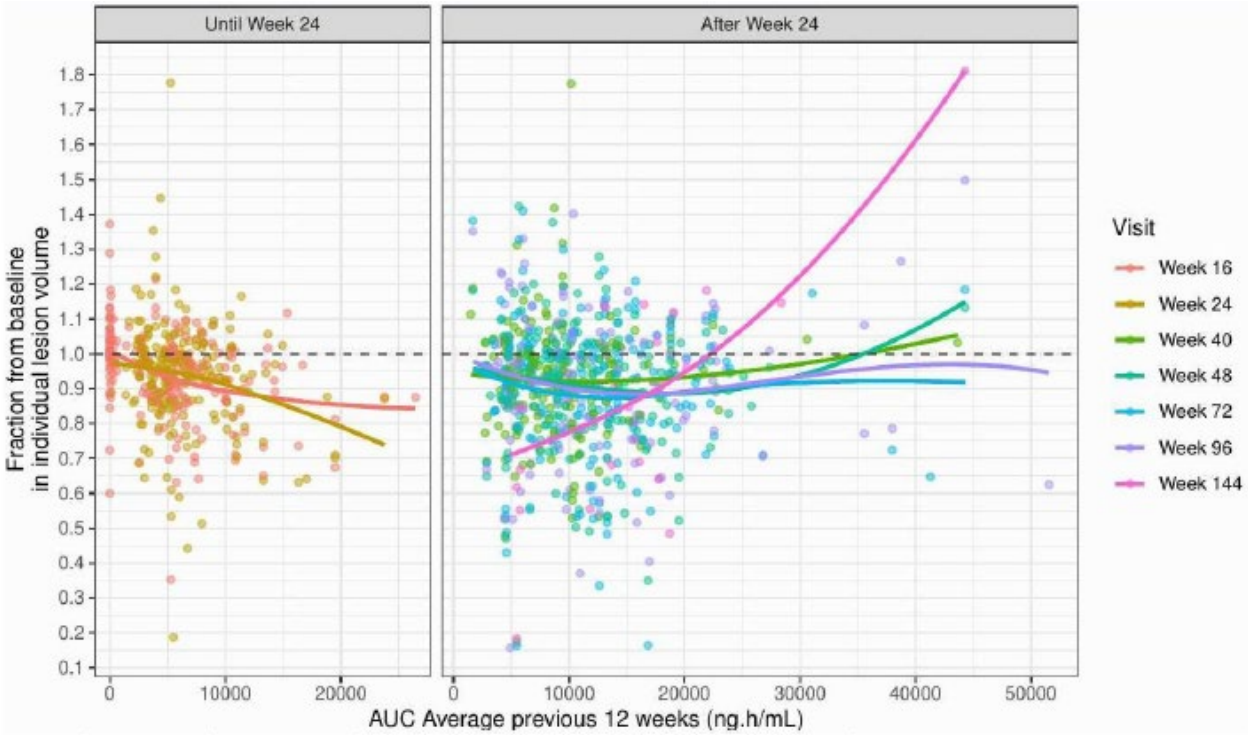
PK/PD modelling

The analysis used the model-predicted exposure (AUCavg, 12weeks) as a PK metric and the fractional change from baseline in individual lesion volume as the PD endpoint. Data included 181 adult patients

and paediatric patients with PROS enrolled in EPIK-P2, with a total of 217 baseline-identified lesions, resulting in 1149 lesion volume measurements. Of these, 408 measurements up to Week 24, and 741 beyond Week 24, when dose escalation was permitted.

Figure 14 displays the fraction from baseline of volume lesions versus AUCavg, 12weeks until Week 24 (left panel) and after Week 24 (right panel). Until Week 24, there is an apparent relationship where larger decreases in individual lesion volumes are associated with higher exposure level across the entire exposure range. By contrast, after Week 24, while the relationships decrease initially, they tend to plateau as approximately 10,000 ng.h/mL at the Week 40 visit and at about 15,000 ng.h/mL at subsequent visits. The atypical relationship at Week 144 must be interpreted cautiously due to the small number of measurements (N=30).

Figure 14. Cross-sectional exposure-response relationship for individual lesion volume during the entire analysis period, by visit.



The dots represent individual data points. The curves represent the mean fraction from baseline in individual lesion volume corresponding to a given exposure, as predicted by a local polynomial regression (loess curve), separately by visit.

The PK/PD assessment was limited to the first 24 weeks, before any dose escalation; to avoid bias in assessment caused by dose increases in non-responders. The final PK/PD model, based on data through Week 24, was a direct effect model with a fixed intercept (1) and a linear exposure effect (kkill) of alpelisib AUCavg,12w on lesion volume change. Its equation is: $F(t) = FFBV0 - kkill \times AUCavg,12w(t)$.

The final model included an additive residual error term (approximately 0.058) and lesion location (leg vs. non-leg) as a covariate on kkill (5.7e-06 versus 1.2e-05 $(ng{\cdot}h/mL)^{-1}$).

Table 11 provides the model parameter estimates of the final Pop-PKPD model of alpelisib.

Goodness-of-fit diagnostic plots for the final model of alpelisib are presented in **Figure 13**, **Figure 14**, **Figure 15** and **Figure 16**. PcVPC is shown in **Figure 12**.

Table 13: Final PD model parameter estimates.

Parameter	Estimate	SE	RSE (%)
Fixed effects (unit)			
$FFBV0$ (unitless)	1	--	--
$kkill$ $((ng.h/mL)^{-1})$	1.2 e-5	1.85 e-06	15.4
Covariate effect on $kkill$			
Individual lesion located in the leg (versus not in the leg)	-6.31 e-6	2.26 e-06	35.9
Standard deviation of the random effects			
$FFBV0$	0.128	0.00703	5.51
Residual error			
Additive	0.0582	0.003	5.15

Figure 15. Fraction from baseline in individual lesion volume: Observation versus IPRED

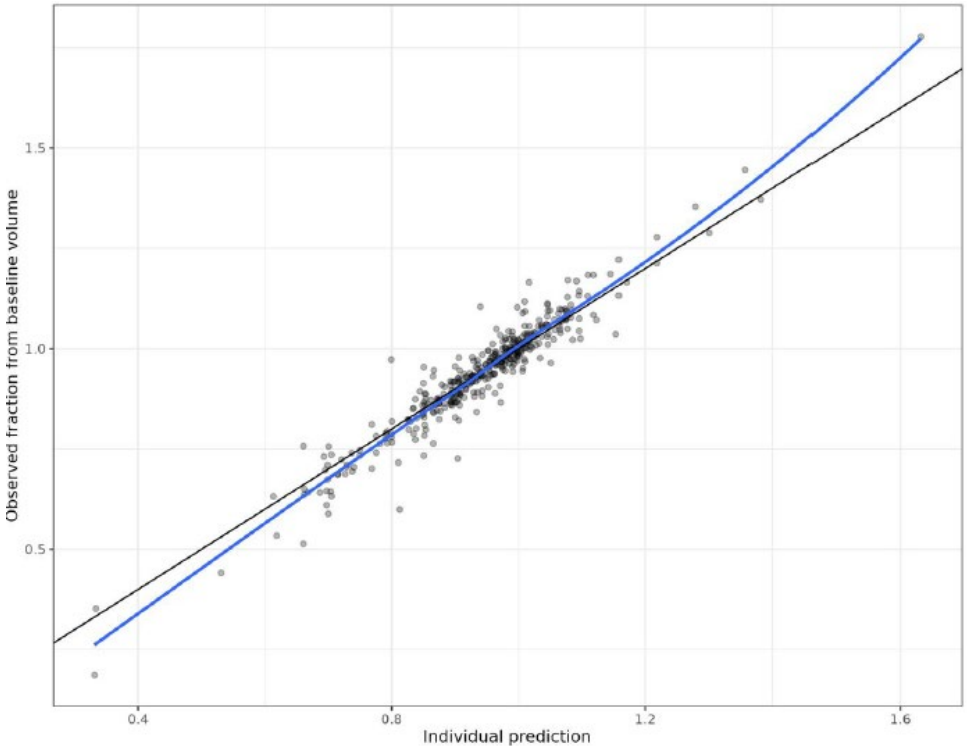
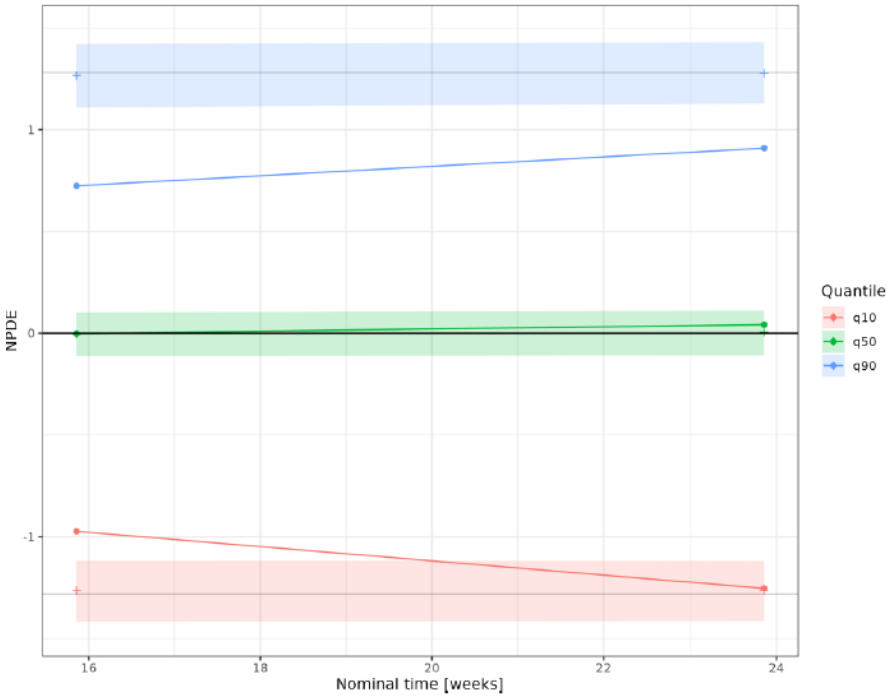


Figure 16. Fraction from baseline in individual lesion volume: NPDE versus nominal time point up to 24 weeks



Note: 3 data points in the popPKPD analysis data set are not included in the figure because they were obtained at an unscheduled visit.

Note: Under the correct model and additional assumptions, the NPDEs are standard normally distributed. If the NPDE sample distribution is skewed towards positive values, this can indicate an underprediction from the model, i.e. the predicted values tend to be smaller than the observed values. Conversely, if the NPDE sample distribution is skewed towards negative values, this can indicate an overprediction from the model, i.e. the predicted values tend to be larger than the observed values.

Figure 17. Fraction from baseline in individual lesion volume: IWRES versus IPRED

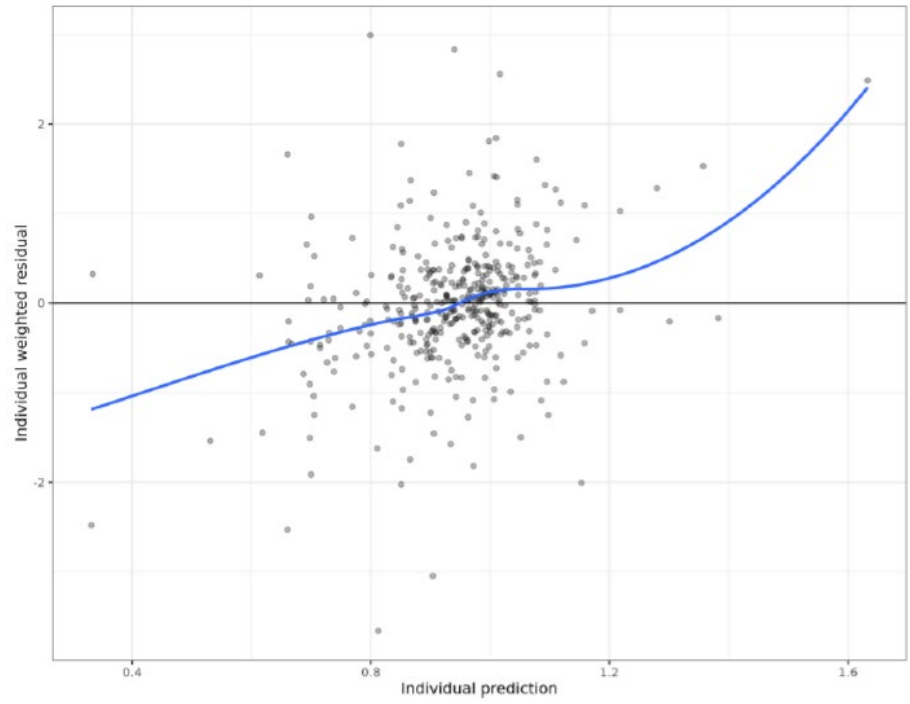
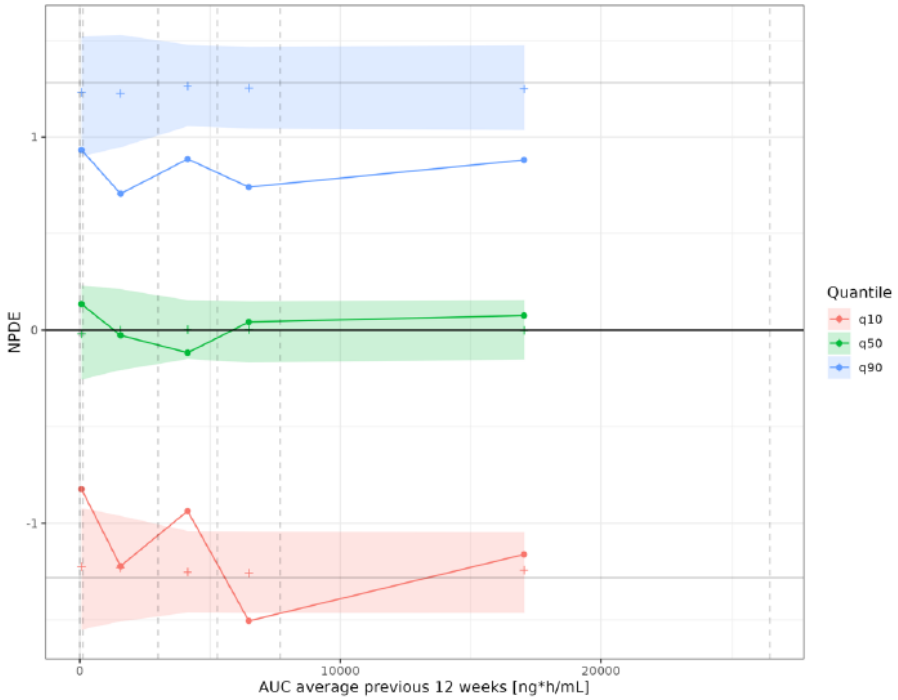
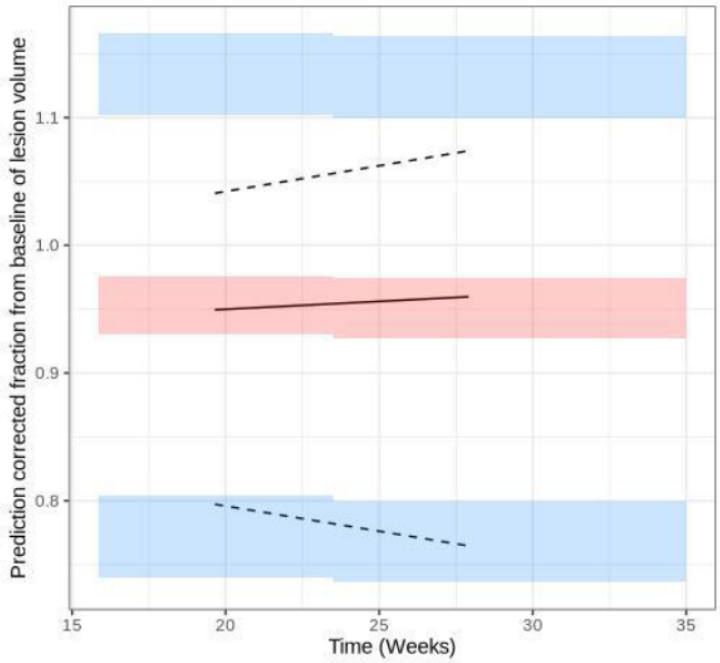


Figure 18. Fraction from baseline in individual lesion volume: NPDE versus alpelisib exposure



Note: Under the correct model and additional assumptions, the NPDEs are standard normally distributed. If the NPDE sample distribution is skewed towards positive values, this can indicate an underprediction from the model, i.e. the predicted values tend to be smaller than the observed values. Conversely, if the NPDE sample distribution is skewed towards negative values, this can indicate an overprediction from the model, i.e. the predicted values tend to be larger than the observed values.

Figure 19. Fraction from baseline in individual lesion volume: prediction-corrected VPC



The middle line (solid) represents the median of the observed fraction from baseline in individual lesion volume data. The bottom and top lines (dashed) represent the corresponding 5th and 95th percentiles. The colored areas represent the 90% predictive intervals for the 5th (bottom blue), 50th (middle red), and 95th (top blue) percentiles of the empirical distribution of the observed fraction from baseline in individual lesion volume data. The CI are obtained by simulations from the popPKPD model.
The predictions are plotted versus the time since the baseline measurement of the individual lesion volume.

Exposure-response (E-R) relationships

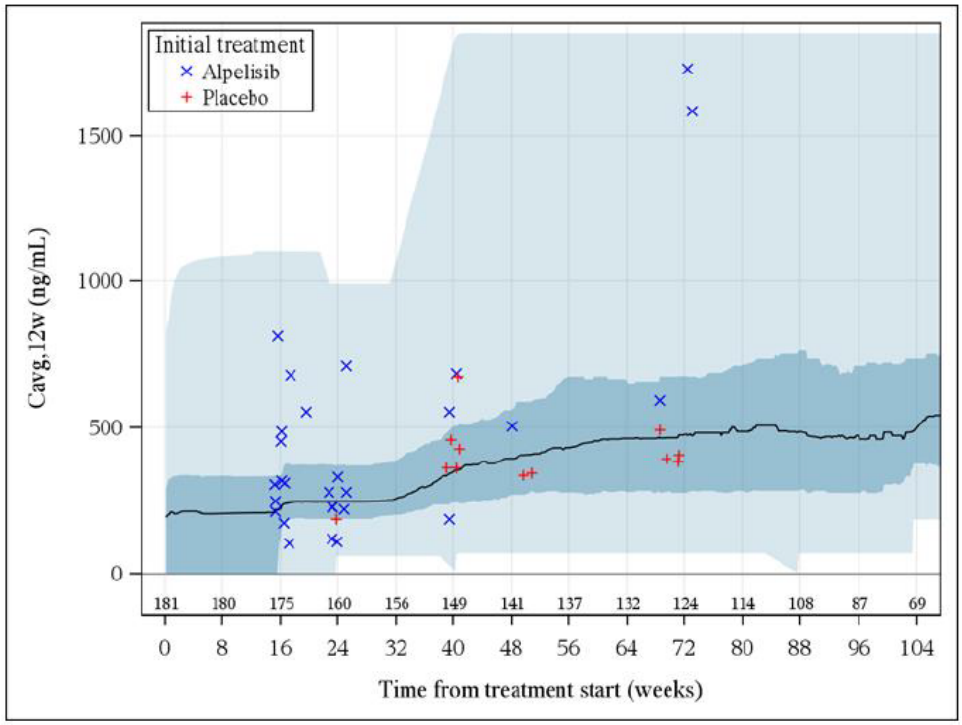
E–R efficacy and safety analyses included 181 PROS patients (including 76 adults ≥18 years, 40 aged 12–<18 years, 58 aged 6–<12 years, and 7 aged 2–<6 years) from EPIK-P2 (cut-off: 25-Sep-2024). Efficacy used Cavg,12w versus confirmed response (defined as achieving a confirmed ≥ 20% reduction from baseline in the sum of target lesion volumes) and safety assessed four AESIs (alopecia, GI toxicity, hyperglycemia, rash) versus Cavg,5d.

Efficacy

Graphical plot showed confirmed responses across the full exposure range (n = 40; 22.1%), including 22 prior to Week 24 (before up-titration). Over the full treatment period, a statistically significant association was observed between higher alpelisib exposure Cavg,12w and increased hazard of confirmed response (HR: 1.19 per 100 ng/mL; 95% CI: 1.06–1.35; p = 0.004), but this was not significant when restricted to data up to Week 24 (HR: 1.17; p = 0.155) (**Table 12**).

Cox regression adjusted for the age (pediatric versus adults) group showed a non-significant trend toward higher response rates in paediatric patients (e.g. HR: 1.49 vs adult patients; 95% CI: 0.78–2.86; p = 0.229), with consistent findings across paediatric subgroups. Model-based predictions after one year of treatment suggested a higher probability of response in paediatrics at similar exposures, with overlapping confidence intervals and lack of statistical significance of age covariate (**Figure 21**).

Figure 20. Alpelisib exposure metric on days with and without confirmed response events.



The numbers of patients at risk are shown at the start of each 8-week period. These numbers include patients who did not have the event (confirmed response) and were not censored before the start of the period.
The blue and red symbols represent the exposure metric ($Cavg$,12w) on a day where the patient experience an event (the x-axis value is the time of event; the y-axis value is the exposure metric on that day). Note that all events in the group of patients randomized to placebo (red symbols) occur after the patients are switched to alpelisib.
The black line represents the median of the exposure metric on each day, in the subset of patients who have not yet experienced event before that day and have no event on that day. The four ribbons represent the 4 quartiles of the exposure metric distribution on each day in the same subset of patients.

Table 14: Final PD model parameter estimates

Analysis period	Response rate	Model parameter	Estimate (SE)	p-value	Hazard ratio[1] Estimate	95% LCL	95% UCL
Full	40/181 (22.1%)	Cavg,12w (ng/mL)	1.78×10^{-3} (0.62×10^{-3})	0.004	1.19	1.06	1.35
Up to Week 24 visit	22/181 (12.2%)	Cavg,12w (ng/mL)	1.56×10^{-3} (1.10×10^{-3})	0.155	1.17	0.94	1.45

Note: The model is an extended Cox regression model for the time to confirmed response, stratified by age group (four age groups are 2-5, 6-11, 12-17 and 18 years and over). Patients in both treatment arms (alpelisib and placebo) are included in the analysis.

[1] Hazard ratio and its corresponding CI for Cavg,12w are for 100 ng/mL increase in Cavg,12w.

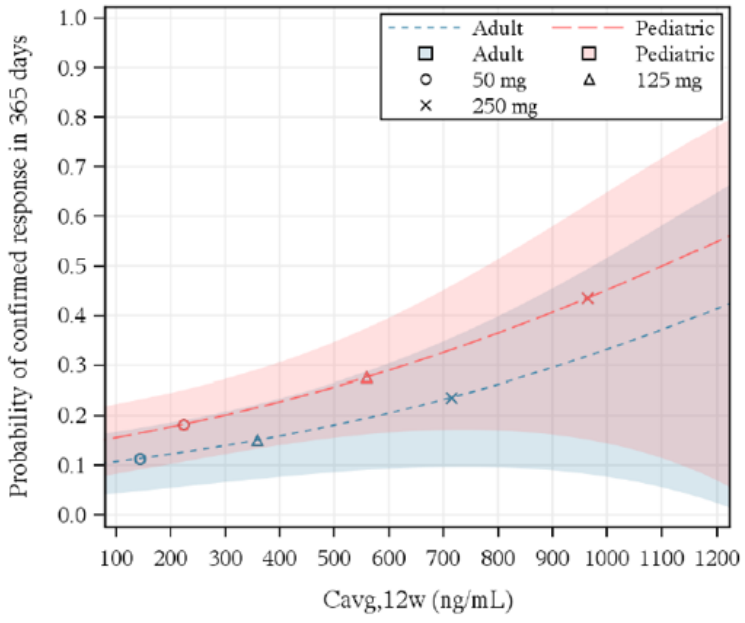
Table 15. Estimate of the time to confirmed response analysis, adjusted for the popPK predicted Cavg,12w and the population (adult versus pediatric).

Analysis period	Response rate	Model parameter	Estimate (SE)	p-value	Hazard ratio[1] Estimate	95% LCL	95% UCL
Full	40/181 (22.1%)	Cavg,12w (ng/mL)	1.41×10^{-3} (0.50×10^{-3})	0.005	1.15	1.04	1.27
		Pediatric vs Adult	0.40 (0.33)	0.229	1.49	0.78	2.86
Up to Week 24 visit	22/181 (12.2%)	Cavg,12w (ng/mL)	1.98×10^{-3} (1.04×10^{-3})	0.056	1.22	0.99	1.49
		Pediatric vs Adult	0.83 (0.50)	0.096	2.28	0.86	6.03

The model is an extended Cox regression model for the time to confirmed response with popPK predicted Cavg,12w and population (adult or pediatric) as covariates. Patients in both treatment arms (alpelisib and placebo) are included in the analysis.

[1] Hazard ratio and the corresponding CI is for Cavg,12w is for 100 ng/mL increase in Cavg,12w (Equation 1 in Section 6.2.3). Hazard ratio for pediatric versus adult are the hazard for pediatric subjects divided by the hazard for adult subjects with same alpelisib exposure (Equation 2 in Section 6.2.3).

Figure 21. Probability of confirmed response by Day 365, as predicted from time to confirmed response analysis, adjusted for the popPK predicted Cavg,12w and the population (adult versus pediatric).

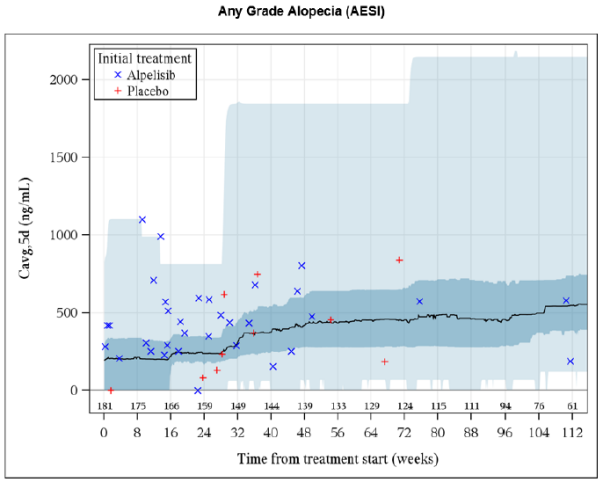


Safety

Figure 22 to **Figure 28** provide a graphical comparison of the distribution of the time varying alpelisib exposure metric Cavg,5d with and without event, for the 4 safety endpoints, any grade and Grade 2 or higher. The plots suggested that more alopecia and rash events (any grade) occurred above the median exposure, with a less evident trend for Grade ≥2 events due to limited numbers.

Cox regression (**Table 14**) stratified by age confirmed a statistically significant association between higher alpelisib exposure Cavg,5d and increased hazard of first alopecia (HR: 1.16 per 100 ng/mL; 95% CI: 1.04–1.29; p = 0.010) and rash (HR: 1.15; 95% CI: 1.02–1.30; p = 0.020). For Grade ≥2 events, hazard estimates were similar but not statistically significant, likely due to low incidence (≤4.4%). No exposure–response was identified for GI toxicity or hyperglycemia (HRs close to 1, p > 0.6).

Figure 22. Alpelisib exposure metric on days with and without alopecia – Any grade



The numbers of patients at risk are shown at the start of each 8-week period. These numbers include patients who did not have the event (any grade alopecia (AESI)) and were not censored before the start of the period.
The blue and red symbols represent the exposure metric ($Cavg,5d$) on a day where the patient experience an event (the x-axis value is the time of event; the y-axis value is the exposure metric on that day). Note that events in the group of subjects randomized to placebo (red symbols) may occur after the subjects are switched to alpelisib.
The black line represents the median of the exposure metric on each day, in the subset of patients who have not yet experienced event before that day and have no event on that day. The four ribbons represent the 4 quartiles of the exposure metric distribution on each day in the same subset of patients.

Figure 23. Alpelisib exposure metric on days with and without alopecia – Grade 2 or higher

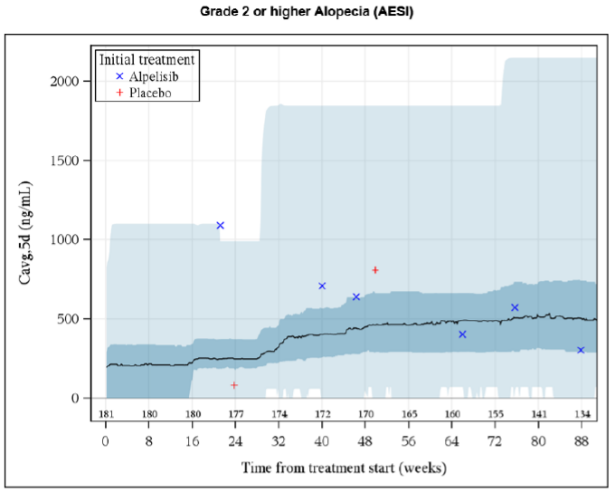


Figure 24. Alpelisib exposure metric on days with and without GI toxicity – Any grade

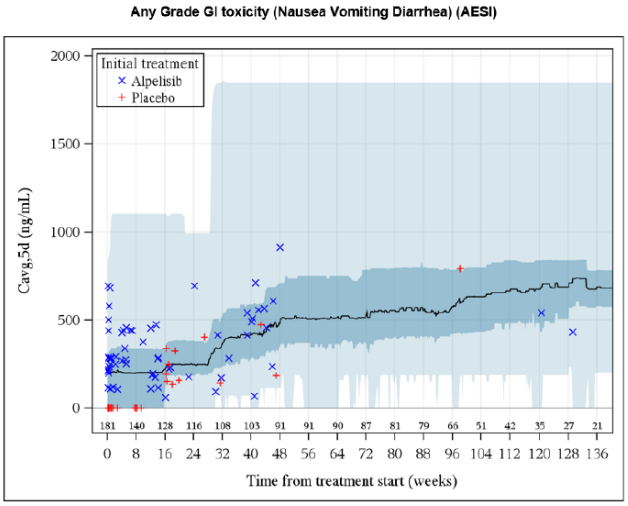


Figure 25. Alpelisib exposure metric on days with and without GI toxicity – Grade 2 or higher

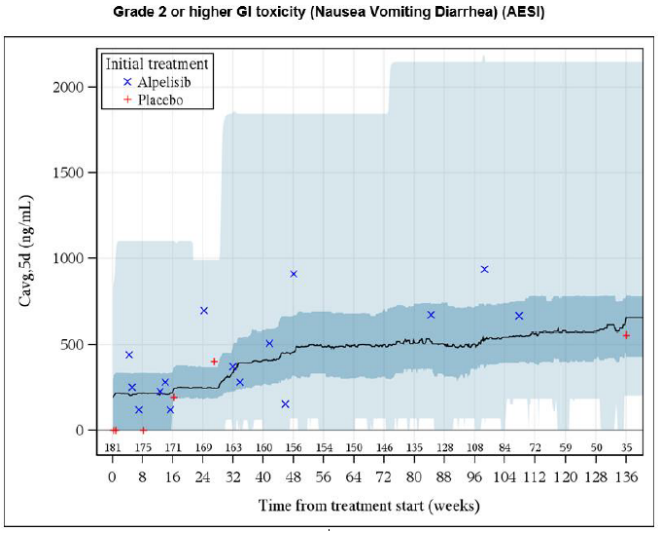


Figure 26. Alpelisib exposure metric on days with and without hyperglycemia – Any grade

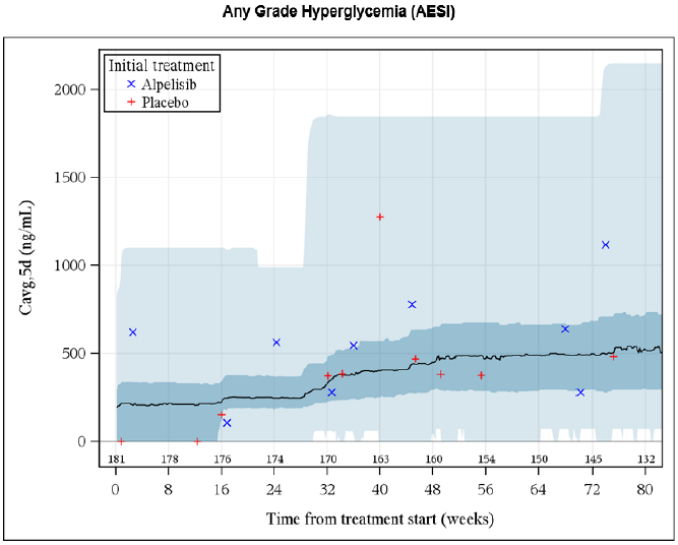


Figure 27. Alpelisib exposure metric on days with and without hyperglycemia – Grade 2 or higher

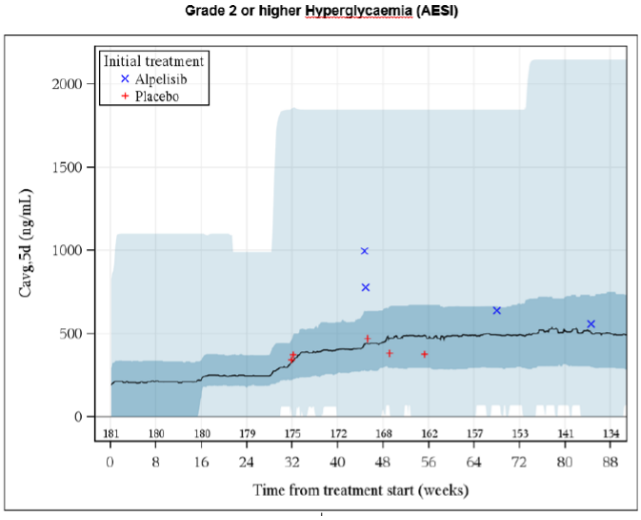


Figure 28. Alpelisib exposure metric on days with and without rash – Any Grade

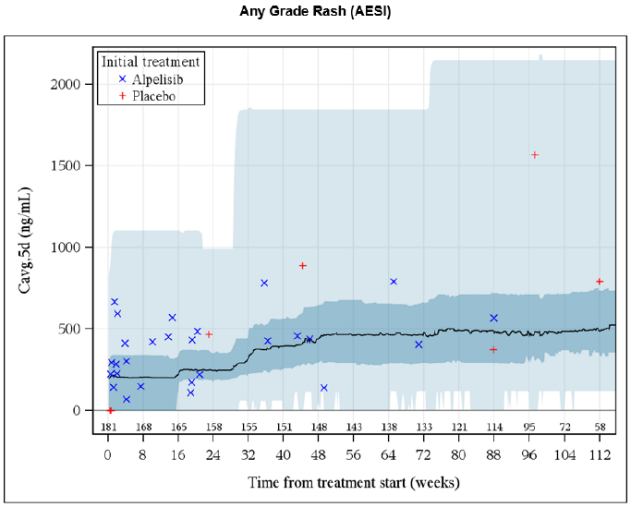


Figure 29. Alpelisib exposure metric on days with and without rash – Grade 2 or higher

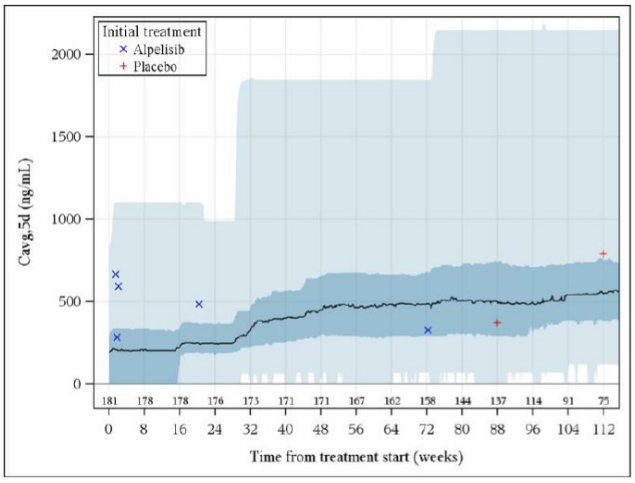


Table 16. Estimate of the time to event analysis for first AESI, adjusted for the Pop-PK predicted Cavg,5d

Endpoint	Grade	Event rate	Model parameter	Estimate (SE)	p-value	Hazard ratio[1] Estimate	95% LCL	95% UCL
Alopecia	Any grade	43/181 (23.8%)	Cavg,5d (ng/mL)	1.47×10^{-3} (0.57×10^{-3})	0.010	1.16	1.04	1.29
	Grade 2 or higher	8/181 (4.4%)	Cavg,5d (ng/mL)	2.24×10^{-3} (1.48×10^{-3})	0.130	1.25	0.94	1.67
GI toxicity	Any grade	88/181 (48.6%)	Cavg,5d (ng/mL)	-0.19×10^{-3} (0.53×10^{-3})	0.724	0.98	0.88	1.09
	Grade 2 or higher	21/181 (11.6%)	Cavg,5d (ng/mL)	0.42×10^{-3} (0.95×10^{-3})	0.656	1.04	0.87	1.26
Hyperglycemia	Any grade	19/181 (10.5%)	Cavg,5d (ng/mL)	0.96×10^{-3} (0.88×10^{-3})	0.271	1.10	0.93	1.31
	Grade 2 or higher	9/181 (5.0%)	Cavg,5d (ng/mL)	0.99×10^{-3} (1.33×10^{-3})	0.454	1.10	0.85	1.43
Rash	Any grade	34/181 (18.8%)	Cavg,5d (ng/mL)	1.43×10^{-3} (0.61×10^{-3})	0.020	1.15	1.02	1.30
	Grade 2 or higher	7/181 (3.9%)	Cavg,5d (ng/mL)	1.37×10^{-3} (1.21×10^{-3})	0.258	1.15	0.90	1.45

Note: The models are extended Cox regression model for the time to first AESI with popPK predicted Cavg,5d as a covariate, stratified by age group (four age groups are 2-5, 6-11, 12-17 and 18 years and over). Patients in both treatment arms (alpelisib and placebo) are included in the analysis. Note that patients in the placebo arms were switched to treatment with alpelisib after 16 weeks.

[1] Hazard ratio for Cavg,5d is for 100 ng/mL increase in Cavg,5d.

5.2.5. Dose selection and therapeutic window

The doses recommended for registration are based primarily on the safety and efficacy data from EPIK-P1 and EPIK-P3, for which no PK data are available.

According to the Applicant, these doses are supported by PK/PD, and ER analyses developed using the exposure and response data from EPIK-P2. For the treatment of severe or life-threatening manifestations of PROS in patients requiring systemic therapy, the recommended dose in adult patients is 250 mg q.d. with food and the recommended starting dose for paediatric patients aged 2 to <18 years is 50 mg q.d. with food, with up-titration to a maximum dose of 125 mg q.d. with food as needed for response optimization in patients aged 6 to <18 years after at least 24 weeks of treatment at 50 mg. Paediatric patients are recommended to gradually increase to the adult dose when 18 years of age is attained.

According to the Applicant, ER and PK/PD modelling indicate a positive relationship between exposure and both PD (individual lesion volume percent change from baseline) and clinical response (confirmed radiological response), indicating the effectiveness of PROS treatment with alpelisib and supporting individualized dose escalation as needed for response optimization in patients aged 6 years and older. Please refer to analyses presented above.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Relative bioavailability / drug administration

A phase Ib study in cancer patients compared the PK of alpelisib administered as a crushed tablet oral suspension versus the intact tablet. While the geometric mean AUC and Cmax were slightly higher (about 20%) with the crushed tablet after both single and repeated doses, formal BE criteria were not met. The

90% CI for the geometric mean ratios of AUC (AUCinf for Day 1 and AUC0-24h for Day 15) and Cmax ([0.77, 1.19] and [0.72- 1.39], respectively), fell outside the [0.80–1.25] acceptance range. Accordingly, the Applicant has removed the unsupported claim of bioequivalence from section 5.2 of the SmPC. The revised wording reports the results of the relative bioavailability comparison without implying formal bioequivalence. Given the close central tendency between the two formulations and the need for an alternative method of administration for patients with swallowing difficulties, administration of crushed tablets as an oral suspension is considered acceptable.

No direct clinical PK comparison was provided for administration via gastric or nasogastric tube versus the intact tablet. However, as administration via feeding tube relies on the same crushed tablet suspension, in vitro data further support the feasibility with minimal drug loss. Taken together, these data support the proposed administration via feeding tube, particularly in patients unable to swallow. The ongoing EPIK-P4 study is expected to further document the impact of administration via feeding tube in clinical practice.

Population-PK analysis

A new Pop-PK model of alpelisib was developed to support the PROS indication, integrating data from oncology and PROS populations, including pediatric patients (2 to 18 years). The Applicant has addressed several points raised at Day 120 by providing additional diagnostics, including bootstrap and η-shrinkage results, and by clarifying the absorption model structure. Clearance and volume parameters are estimated with acceptable precision at the population level, and bootstrap results support numerical stability of the model.

However, key limitations remain. Absorption is still poorly characterised at the individual level, with high η-shrinkage on absorption parameters and systematic under-prediction of Cmax. In addition, the residual proportional error remains high (~42%), and graphical diagnostics (VPC, pcVPC, QPC) indicate limited predictive performance, with broad prediction intervals and persistent bias. While the model appears suitable for descriptive population-level analyses, it is not considered reliable for individual exposure prediction. Consequently, exposure metrics derived from this model are not considered sufficiently robust to support exposure–response analyses.

Impaired renal function

The limited renal excretion of unchanged alpelisib (~2%) suggests minimal renal elimination. Nevertheless, the Pop-PK analysis identified moderate renal impairment as a statistically significant covariate affecting alpelisib apparent clearance (CL/F). In response to the request, the Applicant has provided observed steady-state exposure data (AUC0–24h,ss, Cmax,ss and Cmin,ss) in patients with PROS, stratified by renal function. Higher mean exposures were observed in patients with mild renal impairment compared with normal renal function in both adult and paediatric PROS patients; however, these data are based on very small numbers of patients and are therefore of limited interpretability. Additional popPK analyses indicate that the observed differences are largely driven by body weight imbalance rather than renal function itself. Overall, the newly provided data do not indicate a clinically relevant effect of mild renal impairment on alpelisib exposure. Model-based predictions for moderate renal impairment, derived from oncology data, do not support the need for dose adjustment and could be considered extrapolable to the PROS indication. The absence of PK data in patients with severe renal impairment is now explicitly stated in section 5.2 of the SmPC.

Impaired hepatic function

The conclusion of no dose adjustment in patients with mild, moderate, or severe hepatic impairment (Child-Pugh A, B, and C, respectively), based on the dedicated hepatic impairment study, is considered acceptable and is already reflected in section 5.2 of the SmPC. The additional population PK–based statement on hepatic impairment was removed. This is considered appropriate, as the analysis was

based on non-recommended NCI criteria, included very few subjects (n=5, 0.7%) with moderate hepatic impairment and none with severe impairment, and does not provide meaningful additional information beyond the dedicated study.

Ethnic factors

The Applicant was requested to remove redundant PK statements on race/ethnicity from section 5.2 of the SmPC, in particular references to comparisons between Japanese and Caucasian populations, which are not specific to the PROS indication and are already reflected in the SmPC of Piqray. The requested revisions have now been implemented.

Body weight

BW was identified as a significant covariate affecting both alpelisib CL/F and volume V/F, suggesting that lower BW leads to higher systemic exposure, while higher BW results in lower exposure. The proposed dosing regimen (50 mg for children aged 2-6 years, 125 to 250 for patients 6-17 years and a 250 mg dose for adults) appears to address at least partially this weight effect. From the assessor's perspective, the observed differences in PK across age groups are likely confounded by, or primarily driven by, differences in BW, rather than age per se (age was not retained as a significant covariate in the Pop-PK).

In adults, additional observed steady-state PK data at 125 mg q.d confirmed a clear inverse relationship between BW and systemic exposure. Compared with patients weighing 70–<90 kg, patients weighing 40–<60 kg showed higher exposure (AUC24h,ss +9%; Cmax,ss +29%), whereas patients weighing 90–<130 kg showed substantially lower exposure (AUC24h,ss −36%; Cmax,ss −30%). Model-based predictions at the proposed adult dose of 250 mg were consistent with these findings, although interpretation remains limited by the absence of observed steady-state PK data at the recommended adult dose and by the known limitations of the Pop-PK model. Overall, the magnitude of the BW effect in adults was not considered sufficient to warrant BW-based dose adjustment. The SmPC has been amended to provide a clear description of the effect of BW on alpelisib PK.

In paediatric patients, newly provided observed steady-state PK data at 50 mg once daily (patients aged 6–17 years) demonstrated a pronounced BW effect, with mean AUC24h,ss decreasing from approximately 7250 ng·h/mL in patients <30 kg to 2540 ng·h/mL in patients ≥60 kg (≈65% decrease), and mean Cmax,ss decreasing by approximately 60% over the same BW range. Model-based analyses further confirmed that paediatric patients treated with 50 mg once daily are systematically under-exposed compared with adults receiving 250 mg once daily. While no clear relationship between BW-related exposure differences and clinical efficacy or safety was identified he PK rationale based on systemic exposure matching to the adult reference exposure that would support the selected paediatric doses is lacking. The Applicant acknowledged uncertainties regarding the current paediatric starting dose and indicated that this will be further investigated in the ongoing EPIK-P4 study. The Applicant has revised the SmPC to include a quantitative description of the BW effect on alpelisib exposure in paediatric patients 6–<18 years old. The revised wording is considered acceptable; however, a statement implying a dosing recommendation still remains and should be removed, as it is inconsistent with the observed effect of BW and ongoing refinement of paediatric doses (SmPC comment).

Elderly

No elderly patients with PROS were included in the EPIK-P2 study, and formal PK data are lacking for this subgroup. The assessment of a potential age effect therefore relies on extrapolation from oncology data and Pop-PK analysis integrating both cancer and PROS patients. Based on multiple sensitivity analyses, age was not identified as a clinically relevant covariate, with model-based estimates suggesting a limited impact on alpelisib exposure (<10% difference relative to a 60-year-old reference). In addition, no dose adjustment is recommended in elderly patients treated with alpelisib 300 mg in the approved

oncology indication, supporting consistency across indications. On this basis, the absence of a specific dose adjustment for elderly patients with PROS is considered acceptable from a PK perspective. Section 5.2 has been updated by explicitly stating the lack of clinical PK data in elderly PROS patients.

PK/PD modelling

An exploratory PK/PD analysis was conducted using lesion volume change as the PD endpoint and model-predicted AUC over 12 weeks (AUCavg,12w) as the PK metric. The model was limited to data from the first 24 weeks, before dose escalation, and thus reflects subtherapeutic doses (125 mg in adults, 50 mg in children). While a modest linear PKPD relationship was identified, the model showed limited predictive performance and relied on a Pop-PK model with high residual error (~42%).

Importantly, data beyond Week 24 - corresponding to therapeutic doses (250 mg in adults and 50–125 mg in children aged 6–18 years) - do not support a sustained alpelisib effect on lesion volume reduction, as lesion volumes tended to stabilize or increase beyond Week 96. Overall, the PK/PD data are not considered supportive for dose justification, and their inclusion in the SmPC is not endorsed /warranted.

Exposure-responses relationships

E–R analyses were conducted in 181 PROS patients to assess efficacy (Cavg,12w vs. confirmed response) and safety (Cavg,5d vs. selected alopecia, GI toxicity, hyperglycemia, rash AESIs). A statistically significant association between higher exposure and confirmed response was observed over the full treatment period, but not when limited to the first 24 weeks, during which patients received subtherapeutic doses (125 mg in adults, 50 mg in children aged 6–18 years). These findings may support the adult target dose of 250 mg but conversely, suggest that delayed up-titration in paediatric patients may not be optimal, given limited evidence of efficacy at the initial 50 mg dose.

Significant trends were also observed for alopecia and rash (Cavg,5d), although interpretation is limited by the small event numbers for Grade ≥2. No E-R signal was seen for gastrointestinal toxicity or hyperglycemia.

However, all E–R analyses were based on exposure metrics derived from a Pop-PK model with high residual variability (~42%), undermining confidence in individual exposure predictions. Moreover, no justification was provided for the use of Cavg over more conventional metrics (e.g., AUCss, Cmax,ss). These limitations weaken the value of the E–R data for dose justification and do not support their inclusion in the SmPC.

PB/PK model

The objective of the PBPK modeling was to further characterise the PK of alpelisib including absorption, DDI and dose-exposure relationship in adult and paediatric patients aged 2 years and older with PROS.

Simulations were performed for a 7-day period with once daily administration in fed state replicating the EPIK-2 study to verify the PBPK model for alpelisib. Therefore, based on the short half-life of alpelisib and metabolites, simulations were performed at steady state. The model cannot be verified using the same data that was used to build it; therefore, this is not a real verification of the model, but an internal model validation. Therefore, the current ability of the model for extrapolation purposes is questionable.

The ratio of mean model-predicted versus observed PK parameters (Cmax and AUC) were calculated for single or multiple doses of alpelisib for groups 1, 2 and single dose for group 5. The results showed that all ratios were within the acceptable range (0.8-1.25) except AUC ratio of group 5 (0.766) which includes 6 to 17 years old paediatric patients and 125 mg single dose. This can suggest an inadequate characterization of CYP3A4-mediated clearance since FBT450 exposures are under-estimated. The PBPK evaluation of the FBT450 metabolite shows that all predicted/observed ratios across adult and paediatric

cohorts fall within a 2-fold range, which is generally tolerable for exploratory applications. The model exhibits notable underprediction of AUC in adults at multiple dose (P/O ≈0.55) and in paediatrics at 125 mg single dose (P/O ≈0.55), and overprediction in paediatrics at 50 mg single dose (P/O ≈1.43) and multiple doses (P/O ≈1.21). Therefore, refinement particularly of CYP3A4 ontogeny, metabolite formation fraction would be necessary before relying on this PBPK modelling for labelling impacting decisions. On the other hand, only ratios of observed and predicted predose and 3h concentration of alpelisib and its metabolites were calculated for group 4 (2-<6 years of age). The results showed that most of the values were not within the acceptable range, suggesting the PBPK model is not suitable to describe the PK endpoints in children 2-<6 years of age. Therefore, the current PBPK model is not suitable for establishing dosing recommendations in patients 2-<6 years of age nor <2 years of age.

Dose rationale and justification

The proposed posology (250 mg qd in adults; 50 mg qd with optional up-titration to 125 mg in paediatrics aged 6–18 years; 50 mg qd in paediatrics aged 2–6 years) is not robustly supported by PK/PD or E–R modelling, due to the limited reliability of model-based exposure estimates, the use of subtherapeutic doses in the first 24 weeks, and the absence of sustained PD effect. As such, the dose rationale should primarily rely on the observed efficacy and safety outcomes from the EPIK-P2 study.

PK DDI

No clinical studies were conducted assessing the drug-drug interaction potential between alpelisib and hormonal contraceptives. As a potential human teratogen, in the absence of interaction studies, induction cannot be excluded, therefore warnings for the potential lack of efficacy of hormonal contraceptives was included the SmPC. Furthermore, for a teratogen agent, the absence of a dedicated clinical interaction study with contraceptives typically warrants a warning in 4.6 for lack of data, and a recommendation for women using systemic contraceptive steroids to add a barrier method. Sections 4.4, 4.6 of the SmPC and PL have been updated accordingly.

5.2.6.2. Conclusions

In support of the current submission for the PROS indication, additional PK data were collected in the target PROS population (adults and pediatric patients aged 2–18 years) from the confirmatory EPIK-P2 study. While complete PK profiles were obtained in adults and pediatric patients aged 6–18 years, data in the 2–6 years sub-group were sparse and limited (n=6). Overall, the investigated doses cover the proposed posology, and the observed PK profiles are consistent with the previously established PK characteristics of alpelisib (as reflected in the approved Piqray label for oncology patients). This submission also introduces a new 50 mg granule formulation of alpelisib (in addition to the 50 mg, 125 mg, and 200 mg tablet strengths), supported by a positive BE study versus the 50 mg tablet.

The Pop-PK model is considered suitable for descriptive population-level analyses but not reliable for individual exposure prediction, due to high residual proportional error (~42%), limited predictive performance and systematic under-prediction of individual Cmax.

PK/PD and E–R analyses have been submitted; however, their interpretability is limited due to the dependence on model-derived exposure estimates, the use of sub-therapeutic doses during the initial 24-week treatment period (for the PK/PD data), and the lack of a sustained PD effect. Consequently, these analyses do not provide a robust basis to support the proposed posology, which should instead be

primarily justified by the observed clinical efficacy and safety outcomes. Finally, the provided PBPK model is not considered suitable for paediatric patients aged 2 to 6 years.

5.3. Clinical efficacy

5.3.1. Dose response studies

No formal dose finding study was conducted, the dosage regimen used during the compassionate use program was mostly based on the lowest available strength of alpelisib tablets for paediatric patients (i.e. 50 mg) and on the lowest dosage used in breast cancer clinical trials that were ongoing at that time for adult patients (i.e. 250 mg).

In EPIK-P1 and EPIK P3 studies, alpelisib was administered in adult at a starting dose of 250 mg orally once daily with food; in paediatric patients, alpelisib was administered at a starting dose of 50 mg orally once daily with food both on a continuous dosing schedule.

In the EPIK P2 study, in adult participants, alpelisib was administrated at a dose of 125 mg once daily taken with food which is different from the one proposed in the label (i.e. 250 mg once daily taken with food) and in paediatric patients the initial dose of alpelisib was 50 mg once daily taken with food in line with the one proposed in the label. A dose escalation was allowed in adult and in paediatric patients > 6 years old for response optimization.

5.3.2. Main studies

5.3.2.1. EPIK-P1

Study code	CBYL719F12002
EU CT number	Not applicable
NCT number	NCT04285723
Other identifier(s)	EPIK-P1
Location in eCTD	5.3.5.2

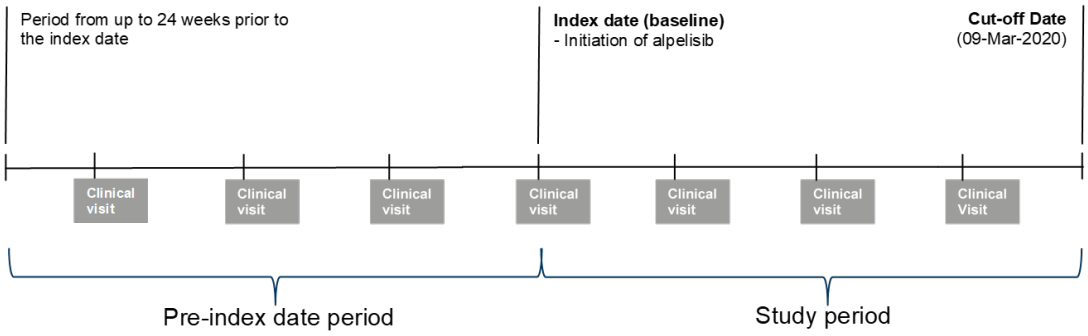
5.3.2.1.1. Study title

Retrospective chart review study of patients with PIK3CA-Related Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK-P1).

5.3.2.1.2. Study design

EPIK-P1 was a site-based retrospective non-interventional medical chart review of patients of 2 years of age and older with severe or life-threatening PROS who have received alpelisib as part of a compassionate use program. This study abstracted data from eligible patients at participating sites that had been previously recorded in the medical charts to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS.

Figure 30 Study schema EPIK-P1



Source: EPIKP1 CSR-Figure 9-1

The index date (baseline) was defined as the date of alpelisib initiation. The pre-index date period was defined as the period from up to 24 weeks prior to the index date through to the day prior to the index date. The study period was defined as the period from the index date up to the cut-off date (09-Mar-2020).

Treatment

In Adult patients, alpelisib was administered at a starting dose of 250 mg orally once daily on a continuous dosing schedule within 1 hour after a meal (preferably in the morning after breakfast) the dose could be adjusted for toxicity.

In paediatric patients, alpelisib was administered at a starting dose of 50 mg orally once daily on a continuous dosing schedule and could be interrupted for toxicity per the recommendations in the treatment plan; no dose reductions were allowed.

Adult patients who experienced adverse events of Grade 3 or higher severity (except hyperglycemia) or did not tolerate the dosing schedule recommended in the Treatment Plan would permanently discontinue treatment. Guidelines for the suggested management of selected toxicities are described below.

Table 17 Dose reduction sequential steps for alpelisib

Alpelisib dose level	Adult dose and schedule	Pediatric dose and schedule
Starting dose	250 mg/day continuously	50 mg/day continuously
Dose level -1	200 mg/day continuously	N/A
Dose level -2	150 mg/day continuously	N/A

Patient population

The study included adult or paediatric patients ⩾ 2 years of age with a physician confirmed/documented diagnosis of PROS, documented evidence of a mutation in the PIK3CA gene1 and when the Patient's condition was assessed by the physician as severe or life threatening and treatment was deemed necessary as part of a compassionate use program.

Patients were included across seven sites in five countries (France (50 patients), Spain (three patients), US (two patients), Ireland (one patient), and Australia (one patient)). Overall, 44 out of 57 patients

(77.2%) were included at the Necker Hospital, Paris, France.

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective of the study was to describe the efficacy of alpelisib as measured by the proportion of patients with radiological response at Week 24 or 6 months (±4 weeks) as determined by an as Independent Central Radiology Review, defined as a $\geqslant$ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions), provided that none of the individual target lesions had $\geqslant$ 20% increase from baseline and in the absence of progression of non-target lesions and without new lesions.

Statistical methods for estimation and sensitivity analysis on primary estimand

The primary and secondary analyses for this study were descriptive in nature (estimation based), and therefore, no hypothesis testing was conducted. All descriptive analyses were presented along with their 95% CIs as appropriate. No estimand approach was used.

Secondary objectives

- Changes in the sum of measurable target lesion (1 to 3 lesions) volume over time
- Changes in the sum of all measurable (target and non-target) lesion volume over time
- Changes in the sum of all measurable non-target lesion volume over time
- Duration of response (DOR) defined as the time from first documented response to the date of the first documented disease progression or death due to any cause
- Changes in medication and non-drug therapies (e.g. concomitant PROS related medications, PROS related surgeries, duration of treatment/response) over time
- Changes in PROS symptoms and complications (e.g. chronic bleeding/leaking, pain) over time
- Changes in functional status (e.g. work/school/pre school attendance, mobility) over time
- Changes in healthcare resource use (HRU) (e.g. ER visits, hospitalizations) over time
- Changes in clinical assessments such as laboratory evaluations, vital signs, and physical findings over time
- Safety and tolerability of alpelisib.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

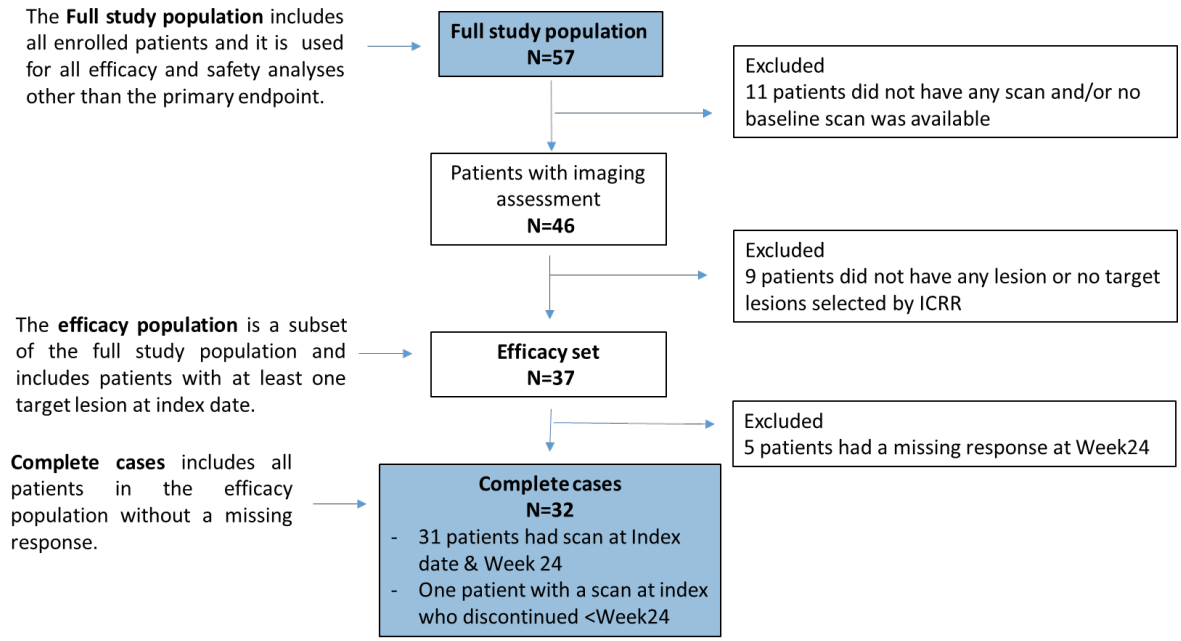
Three sensitivity analyses were performed using multiple imputation method (for missing volumetric assessments at Week 24), a best-case scenario approach (where missing responses at 24 weeks or 6 months were considered as 'responders') and a worst-case scenario approach (where missing responses at 24 weeks or 6 months were considered as 'non-responders').

5.3.2.1.4. Results

Participant flow and numbers analysed

A total of 58 patients were included in EPIK-P1 of whom 57 patients were included in the Full study population (1 patient withdrew consent prior to data collection), including 18 adults and 39 paediatric patients. The details of patients included in each of the analysis populations is depicted in Figure 31.

Figure 31 Participant flow



Source: EPIKP1 CSR-Figure 10-1

The numbers of patients in the Efficacy population at Week 24 by age category are presented in Table 16.

Table 18 Efficacy population at Week 24 (Full study population)

Analysis set Reason	2-5 years N=11 n (%)	6-11 years N=12 n (%)	12-17 years N=16 n (%)	Paediatric patients (<18 years) N=39 n (%)	Adult patients (≥18 years) N=18 n (%)	All patients N=57 n (%)
Efficacy population	8 (72.7)	8 (66.7)	10 (62.5)	26 (66.7)	11 (61.1)	37 (64.9)
Excluded	3 (27.3)	4 (33.3)	6 (37.5)	13 (33.3)	7 (38.9)	20 (35.1)

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis. The Efficacy population is a subset of the Full study population and includes patients with at least one target lesion; patients with an imaging scan performed on the index date (or up to Week 24 prior to the index date) for at least one target lesion. Week 24 windows (± 4 weeks) are intended as Week 24 or 6 months after the index date, where 6 months is approximated to Week 27.

Source: EPIK-P1 CSR-Table 10-3

Deviations from study plan

The changes implemented in this protocol amendment included the specification of a cut-off date (09 Mar 2020) to define the sample of patients to be included in the study to minimize the impact of the SARS CoV 2 (COVID 19) pandemic on the study integrity. The assessment of response status was not expected to be impacted as all patients initiated alpelisib at least 24 weeks before 09 Mar 2020. This resulted in an update to the inclusion criteria.

In the original protocol, the primary analysis applied imputation of the missing volumetric assessments for target lesions at Week 24 (± 4 weeks), while in the amended protocol a complete case analysis was utilized. The complete case analysis was performed based on patients without missing response. The analysis using imputed data was to be performed as a sensitivity analysis (instead of as the primary analysis).

DOR was added to the secondary objectives as it is considered an important measure for assessing the benefit of alpelisib.

For the analysis of the secondary endpoints related to growth and development information were added to better characterize clinical assessments in patients who were aged <18 years at the time of alpelisib initiation.

Baseline data

The median age of the patients was 14 years (range: 2 to 50 years). Most of the patients were paediatrics' patients (39 patients, 68.4%) including 11 patients aged 2 to 6 years old. No elderly patients were included.

Table 19 Demographics and clinical characteristics at index date by age category (Full study population)

Demographic variable	2-5 years N=11	6-11 years N=12	12-17 years N=16	Paediatric patients (<18 years) N=39	Adult patients (≥18 years) N=18	All patients N=57
Age (years)						
n	11	12	16	39	18	57
Mean (SD)	3.6 (1.21)	9.1 (1.44)	14.8 (1.57)	9.9 (4.84)	27.8 (8.34)	15.5 (10.39)
Median	3.0	9.0	15.0	10.0	25.5	14.0
Q1-Q3	3.0-5.0	8.0-10.0	14.0-16.0	5.0-14.0	22.0-32.0	9.0-22.0
Min-Max	2-5	7-11	12-17	2-17	18-50	2-50
Sex-n (%)						
Female	8 (72.7)	6 (50.0)	10 (62.5)	24 (61.5)	9 (50.0)	33 (57.9)
Male	3 (27.3)	6 (50.0)	6 (37.5)	15 (38.5)	9 (50.0)	24 (42.1)
Race-n (%)						
Not reported	10 (90.9)	9 (75.0)	13 (81.3)	32 (82.1)	18 (100)	50 (87.7)
White	1 (9.1)	3 (25.0)	3 (18.8)	7 (17.9)	0	7 (12.3)
Ethnicity-n (%)						
Not reported	5 (45.5)	6 (50.0)	10 (62.5)	21 (53.8)	14 (77.8)	35 (61.4)
Unknown	5 (45.5)	3 (25.0)	2 (12.5)	10 (25.6)	4 (22.2)	14 (24.6)
Not Hispanic or Latino	1 (9.1)	2 (16.7)	2 (12.5)	5 (12.8)	0	5 (8.8)
Hispanic or Latino	0	1 (8.3)	2 (12.5)	3 (7.7)	0	3 (5.3)
Weight (kg)						

Demographic variable	2-5 years N=11	6-11 years N=12	12-17 years N=16	Paediatric patients (<18 years) N=39	Adult patients (≥18 years) N=18	All patients N=57
n	8	8	13	29	15	44
Mean (SD)	18.49 (6.053)	38.76 (11.392)	56.19 (15.007)	40.98 (19.787)	84.48 (31.376)	55.81 (31.788)
Median	17.10	42.55	55.90	42.80	73.60	53.25
Q1-Q3	14.10-21.05	30.70-45.25	46.00-60.70	23.50-54.60	58.60-118.60	35.30-68.20
Min-Max	12.7-30.7	18.5-54.6	39.2-97.0	12.7-97.0	45.7-141.3	12.7-141.3
Height (cm)						
n	9	8	11	28	8	36
Mean (SD)	103.5 (12.28)	138.7 (12.29)	160.1 (10.29)	135.8 (26.71)	169.8 (10.14)	143.3 (27.85)
Median	102.0	144.3	161.7	144.3	171.0	148.0
Q1-Q3	96.0-106.0	132.2-147.5	157.0-170.0	110.0-157.0	161.0-176.5	122.5-164.5
Min-Max	89-123	114-148	138-172	89-172	156-185	89-185
Body mass index (kg/m^2)						
n	8	7	11	26	8	34
Mean (SD)	16.84 (2.134)	20.76 (4.264)	21.98 (4.913)	20.07 (4.513)	24.32 (6.003)	21.07 (5.140)
Median	16.67	21.23	20.58	20.05	22.74	20.19
Q1-Q3	15.74-18.12	16.73-25.27	19.34-23.53	16.73-21.67	19.00-29.08	17.04-23.49
Min-Max	13.4-20.3	14.2-26.1	15.9-34.8	13.4-34.8	18.3-34.7	13.4-34.8
ECOG performance status-n (%)						
0	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
2	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
3	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Missing	11 (100)	11 (91.7)	14 (87.5)	36 (92.3)	18 (100)	54 (94.7)
Lansky-n (%)						
10-40	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
40-50	3 (27.3)	1 (8.3)	1 (6.3)	5 (12.8)	0	5 (8.8)
60-70	3 (27.3)	1 (8.3)	5 (31.3)	9 (23.1)	0	9 (15.8)
80-90	2 (18.2)	5 (41.7)	0	7 (17.9)	0	7 (12.3)
100	0	0	2 (12.5)	2 (5.1)	0	2 (3.5)
Missing	3 (27.3)	4 (33.3)	8 (50.0)	15 (38.5)	18 (100)	33 (57.9)
Karnofsky-n (%)						
10-40	0	0	0	0	1 (5.6)	1 (1.8)
40-50	0	0	2 (12.5)	2 (5.1)	5 (27.8)	7 (12.3)
60-70	1 (9.1)	0	3 (18.8)	4 (10.3)	3 (16.7)	7 (12.3)
80-90	0	1 (8.3)	2 (12.5)	3 (7.7)	2 (11.1)	5 (8.8)
100	0	0	0	0	2 (11.1)	2 (3.5)
Missing	10 (90.9)	11 (91.7)	9 (56.3)	30 (76.9)	5 (27.8)	35 (61.4)

Source: EPIK-P1 CSR-Table 10-4

Disease history

Overall, patients had heterogeneous manifestations of PROS. The sub-type of PROS reported in the majority of the patients (42 patients, 73.7%) was CLOVES. The median time since a confirmed diagnosis of PROS was 14 years (range: 2 to 50 years).

Table 20 PROS disease history at the index date by age category (Full study population)

Disease history	2-5 yrs N=11	6-11 yrs N=12	12-17 yrs N=16	Paediatric patients (<18 yrs) N=39	Adult patients (≥18 yrs) N=18	All patients N=57
Time since confirmed diagnosis (years)						
n	11	12	16	39	18	57
Mean (SD)	3.6 (1.21)	8.8 (1.99)	14.1 (2.62)	9.5 (4.81)	27.8 (8.34)	15.3 (10.52)
Median	3.0	9.0	14.5	10.0	25.5	14.0
Min - Max	2 – 5	4 - 11	7 - 17	2 - 17	18 - 50	2 - 50
Onset of disease-n (%)						
Congenital overgrowth	11 (100)	11 (91.7)	16 (100)	38 (97.4)	15 (83.3)	53 (93.0)
Early childhood-onset of overgrowth	0	1 (8.3)	0	1 (2.6)	3 (16.7)	4 (7.0)
Overgrowth type-n (%)						
Mosaic distribution	10 (90.9)	12 (100)	16 (100)	38 (97.4)	18 (100)	56 (98.2)
Sporadic occurrence	1 (9.1)	0	0	1 (2.6)	0	1 (1.8)
PROS subtype-n (%)						
CLOVES	7 (63.6)	7 (58.3)	13 (81.3)	27 (69.2)	15 (83.3)	42 (73.7)
MCAP	4 (36.4)	2 (16.7)	2 (12.5)	8 (20.5)	0	8 (14.0)
KTS	0	1 (8.3)	1 (6.3)	2 (5.1)	3 (16.7)	5 (8.8)
FIL	1 (9.1)	2 (16.7)	0	3 (7.7)	0	3 (5.3)
OTHER	0	1 (8.3)	1 (6.3)	2 (5.1)	0	2 (3.5)
MCM	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis. Time since confirmed diagnosis (years) = (Date of diagnosis – index date +1)/365.25. Date of diagnosis is the date as entered in the eCRF. A patient may have multiple PROS subtypes.
Source: EPIK-P1 CSR-Table 10-5)

Outcomes and estimation

Primary efficacy endpoint: Proportion of patients with response at Week 24

The efficacy population included 37 patients (64.9%) from the Full study population, of which, 32 patients were considered for the primary analysis (complete case analysis).

Table 21 Proportion of responders at Week 24 with complete cases (Efficacy population)

All patients N=32		
Category	**n (%)**	**(95% CI)**
Responders	12 (37.5)	(21.1, 56.3)

Non responders	20 (62.5)	(43.7, 78.9)

- 2-sided 95% Confidence Intervals (CI) are based on the exact (Clopper-Pearson) method.
- The proportion of patients with response is defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume provided that none of the individual target lesions have ≥ 20% increase and in absence of progression of non-target lesions and without new lesions.
- Complete cases are defined as the patients in the Efficacy population without a missing response.

Table 22 Proportions of responders at Week 24 with complete cases - subgroup analyses (Efficacy population)

	Responders		Non-Responders	
Category	**n (%)**	**(95% CI)**	**n (%)**	**(95% CI)**
PROS subtype				
CLOVES - (N=26)	12 (46.2)	(26.6, 66.6)	14 (53.8)	(33.4, 73.4)
FIL [Facial Infiltrating Lipomatosis] - (N=3)	0	(0.0, 70.8)	3 (100)	(29.2, 100.0)
KTS [Klippel-Trenaunay Syndrome] - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
MCAP [Megalencephaly-Capillary Malformation] - (N=3)	0	(0.0, 70.8)	3 (100)	(29.2, 100.0)
Other - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
Mutation type				
Frequent - (N=23)	12 (52.2)	(30.6, 73.2)	11 (47.8)	(26.8, 69.4)
Less-frequent - (N=9)	0	(0.0, 33.6)	9 (100.0)	(66.4, 100.0)
Lesion type				
Abdominal region - (N=10)	7 (70.0)	(34.8, 93.3)	3 (30.0)	(6.7, 65.2)
Brain - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
Chest - (N=2)	1 (50.0)	(1.3, 98.7)	1 (50.0)	(1.3, 98.7)
Head - (N=5)	0	(0.0, 52.2)	5 (100)	(47.8, 100.0)
Limb - (N=2)	0	(0.0, 84.2)	2 (100)	(15.8, 100.0)
Lower leg - (N=10)	4 (40.0)	(12.2, 73.8)	6 (60.0)	(26.2, 87.8)
Neck - (N=2)	0	(0.0, 84.2)	2 (100)	(15.8, 100.0)
Other - (N=1)	1 (100)	(2.5, 100.0)	0	(0.0, 97.5)
Pelvis - (N=7)	4 (57.1)	(18.4, 90.1)	3 (42.9)	(9.9, 81.6)
Skin - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
Spinal/paraspinal - (N=2)	1 (50.0)	(1.3, 98.7)	1 (50.0)	(1.3, 98.7)
Upper arm - (N=2)	1 (50.0)	(1.3, 98.7)	1 (50.0)	(1.3, 98.7)
Upper leg - (N=2)	0	(0.0, 84.2)	2 (100)	(15.8, 100.0)
Age (years)				
2-5 - (N=7)	2 (28.6)	(3.7, 71.0)	5 (71.4)	(29.0, 96.3)
6-11 - (N=7)	1 (14.3)	(0.4, 57.9)	6 (85.7)	(42.1, 99.6)
12-17 - (N=9)	4 (44.4)	(13.7, 78.8)	5 (55.6)	(21.2, 86.3)
<18 - (N=23)	7 (30.4)	(13.2, 52.9)	16 (69.6)	(47.1, 86.8)
≥18 - (N=9)	5 (55.6)	(21.2, 86.3)	4 (44.4)	(13.7, 78.8)
Sex				
Male - (N=13)	5 (38.5)	(13.9, 68.4)	8 (61.5)	(31.6, 86.1)
Female - (N=19)	7 (36.8)	(16.3, 61.6)	12 (63.2)	(38.4, 83.7)

- 2-sided 95% Confidence Intervals (CI) are based on the exact (Clopper-Pearson) method.

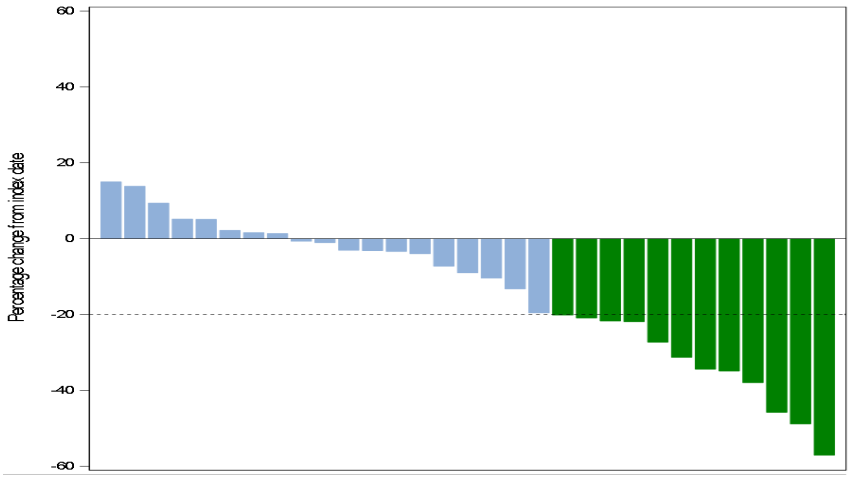
- The proportion of patients with response defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume provided that none of the individual target lesions have ⩾ 20% increase and in absence of progression of non-target lesions and without new lesions.
- Complete cases are defined as the patients in the efficacy population without a missing response.
- Patients are considered as having a missing response if lesion volume(s) assessment at 24 weeks or 6 months (± 4 weeks) is not available and did not permanently discontinue alpelisib prior to 24 weeks of treatment and did not require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.
- PROS subtypes were grouped as recorded in the eCRF. Patients may have more than one subtype. Lesion type refers to the anatomical location of the lesion selected by ICRR. Patients may have more than one lesion type
Table 14.2-2.3

Secondary efficacy analysis

Change in sum of measurable lesion volume

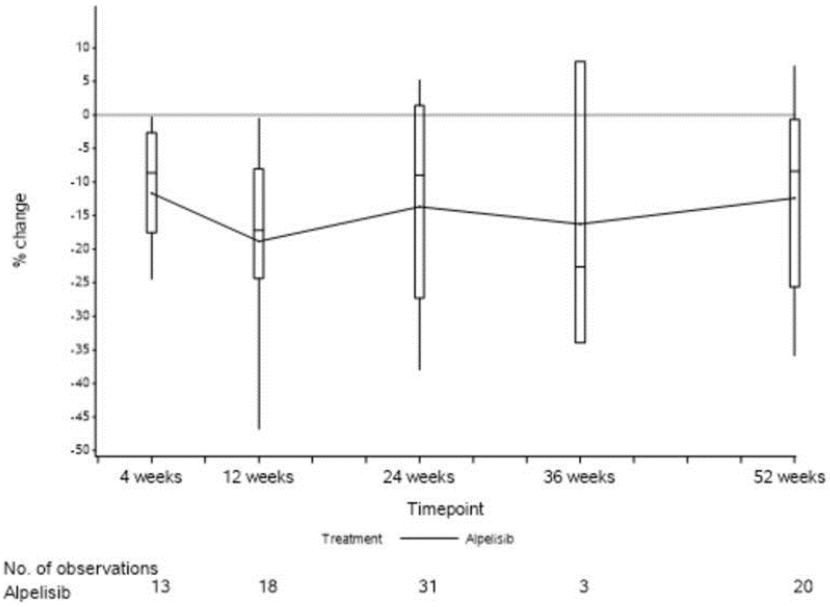
The mean percentage change in the sum of target lesion volume from the index date at Week 24 was -13.7% (range: -57.1% to 15.0%) across the 31 patients with imaging assessments (Figure 32).

Figure 32 Individual percentage change in sum of target lesion (mL) volume at Week 24- EPIK-P1 (Efficacy population)



Patients who are responders for the primary endpoint are highlighted in green. Non-responders are highlighted in blue.
Source: BYL719 PROS SCE-Figure 3-1

Figure 33 Box plot of percent mean change in the sum of target lesions over time (Full study population)



Plot shows boxes (25th-75th percentiles) with median as horizontal line. The dots in the boxes and joint lines represent the percent mean change. Whiskers (vertical lines) extend to the 10th-90th percentiles. Values outside this range are not displayed.
Source: Figure 14.2-1.3

Duration of response (DOR)

The median DOR was not estimable as no events (progression or death) were reported at the time of the data cut-off date.

Table 23 Summary of duration of response by age category (Efficacy population)

	Pediatric patients (<18 years) N=7 n (%)	Adult patients (≥18 years) N=5 n (%)	All patients N=12 n (%)
n/N (%)	0/7 (0.0)	0/5 (0.0)	0/12 (0.0)
Maximum follow-up (weeks)	129.1	186.7	186.7
Median follow-up (weeks)	92.1	3.9	63.3
Median time to censoring (weeks)	92.1	3.9	63.3
Percentiles (95% CI)			
25th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
50th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
75th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
% Distribution of duration of response (95% CI)			
12 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
24 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
36 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
52 weeks	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)

Number (N) represents total number of patients included in the analysis (responders). n: Total number of events included in the analysis.
Response is defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume provided that none of the individual target lesions have ≥ 20% increase and in absence of progression of non-target lesions and without new lesions. Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). Distribution of duration of response estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
In DOR, the start date is the date of first documented response, and the end date is defined as the date of disease progression or death due to any cause. Patients continuing without event were censored at the date of their last adequate lesion assessment.
Source: Table 14.2-2.5

Concomitant PROS-related medications

Pre-index period

Forty-two patients (73.7%) were administered PROS-related medication during the 24 weeks of the pre-index period.

Study period

Overall, during the study period, 45 patients (78.9%) had at least one concomitant medication of which 38 patients received PROS-related medication.

Over time, PROS-related medications were administered in 34/57 patients (59.6%) at the index date, in 30/56 patients (53.6%) at Week 24 and in 25/57 patients (43.9%) at the end of study.

Concomitant medications to treat alpelisib complications any time during the study were received by 8/57 patients. The following concomitant medications were used for treating alpelisib complications: insulin, repaglinide and metformin to treat hyperglycaemia, minoxidil and cystine to treat alopecia, hexetidine mouth wash to treat stomatitis.

Pain medications

The numbers of patients receiving pain medication (including opioids) remained stable from the index date to the end of the study (index date: 18/57 patients, 31.6%; vs. Week 24: 17/56 patients, 30.4%; vs. Week 52: 13/52 patients, 25%; vs. Week 74: 9/38 patients, 23.7%).

Table 24 Concomitant PROS-related medications (used in more than 5 percent of patients) over time during the study period, by ATC class and PT (Full study population)

ATC class Preferred term	Index date N=57	12 weeks N=57	24 weeks N=56	52 weeks N=52	End of study N=57
Number of patients with at least one medication	40 (70.2)	41 (71.9)	37 (66.1)	34 (65.4)	31 (54.4)
Management of a complication related to					
PROS	34 (59.6)	35 (61.4)	30 (53.6)	27 (51.9)	25 (43.9)
Alpelisib	0	4 (7.0)	5 (8.9)	6 (11.5)	7 (12.3)
Other	13 (22.8)	15 (26.3)	14 (25.0)	13 (25.0)	14 (24.6)
Unknown	3 (5.3)	4 (7.0)	4 (7.1)	4 (7.7)	4 (7.0)
Any ATC class					
Total	40 (70.2)	41 (71.9)	37 (66.1)	34 (65.4)	31 (54.4)
ALIMENTARY TRACT AND METABOLISM	17 (29.8)	19 (33.3)	16 (28.6)	16 (30.8)	12 (21.1)
Colecalciferol	6 (10.5)	6 (10.5)	5 (8.9)	4 (7.7)	5 (8.8)
Macrogol	6 (10.5)	6 (10.5)	4 (7.1)	4 (7.7)	1 (1.8)
Lactulose	3 (5.3)	2 (3.5)	2 (3.6)	2 (3.8)	0
Cystine;pyridoxine hydrochloride	0	1 (1.8)	1 (1.8)	3 (5.8)	3 (5.3)
ANTIINFECTIVES FOR SYSTEMIC USE	6 (10.5)	10 (17.5)	8 (14.3)	8 (15.4)	7 (12.3)
Phenoxymethylpenicillin	2 (3.5)	3 (5.3)	3 (5.4)	2 (3.8)	2 (3.5)
Amoxicillin;clavulanic acid	1 (1.8)	1 (1.8)	3 (5.4)	1 (1.9)	2 (3.5)
BLOOD AND BLOOD FORMING ORGANS	16 (28.1)	18 (31.6)	15 (26.8)	14 (26.9)	15 (26.3)
Fondaparinux sodium	5 (8.8)	7 (12.3)	6 (10.7)	6 (11.5)	6 (10.5)
Apixaban	3 (5.3)	3 (5.3)	3 (5.4)	3 (5.8)	2 (3.5)
Folic acid	3 (5.3)	3 (5.3)	1 (1.8)	1 (1.9)	1 (1.8)
Ferrous sulfate	2 (3.5)	3 (5.3)	3 (5.4)	3 (5.8)	2 (3.5)
CARDIOVASCULAR SYSTEM	5 (8.8)	5 (8.8)	5 (8.9)	7 (13.5)	5 (8.8)
DERMATOLOGICALS	3 (5.3)	5 (8.8)	7 (12.5)	6 (11.5)	6 (10.5)
GENITO URINARY SYSTEM AND SEX HORMONES	2 (3.5)	1 (1.8)	2 (3.6)	4 (7.7)	4 (7.0)
MUSCULO-SKELETAL SYSTEM	11 (19.3)	11 (19.3)	11 (19.6)	6 (11.5)	7 (12.3)
Ibuprofen	6 (10.5)	6 (10.5)	6 (10.7)	2 (3.8)	3 (5.3)
NERVOUS SYSTEM	19 (33.3)	21 (36.8)	18 (32.1)	14 (26.9)	15 (26.3)
Paracetamol	8 (14.0)	8 (14.0)	6 (10.7)	4 (7.7)	4 (7.0)
Tramadol	4 (7.0)	5 (8.8)	4 (7.1)	3 (5.8)	4 (7.0)
Gabapentin	3 (5.3)	3 (5.3)	3 (5.4)	3 (5.8)	3 (5.3)
RESPIRATORY SYSTEM	6 (10.5)	7 (12.3)	5 (8.9)	6 (11.5)	5 (8.8)
Salbutamol	3 (5.3)	3 (5.3)	1 (1.8)	1 (1.9)	2 (3.5)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	5 (8.8)	8 (14.0)	5 (8.9)	5 (9.6)	6 (10.5)

A patient may have multiple information for same time window.
The lowest ATC class and preferred term are used. ATC classes are presented alphabetically; preferred terms are sorted by descending frequency at index date.
A medication / therapy can appear with more than one ATC class.
The last interval, referred to as "End of study" will include data available within the last 4 weeks prior to study treatment discontinuation plus 30 days or cut-off date, whichever comes first.
Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
WHODD version WHODD G 01MAR2020.
Source: Table 14.3-2.10

Sub-group analysis of the primary endpoint

All 12 patients who responded to treatment at Week 24 had CLOVES (12/26 patients, 46.2%) as a PROS sub-type. Of the 23 patients with frequent mutation type 12 patients (52.2%) were responders. Response rate was slightly higher in the adult population (5/9 patients, 55.6%) than in the paediatric population (7/23 patients, 30.4%) (Table 23).

Table 25: Proportions of responders at Week 24 with complete cases subgroup analyses (Efficacy population)

Category	Responders n (%)	Responders (95% CI)	Non-Responders n (%)	Non-Responders (95% CI)
PROS subtype				
CLOVES - (N=26)	12 (46.2)	(26.6, 66.6)	14 (53.8)	(33.4, 73.4)
FIL [Facial Infiltrating Lipomatosis] - (N=3)	0	(0.0, 70.8)	3 (100)	(29.2, 100.0)
KTS [Klippel-Trenaunay Syndrome] - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
MCAP [Megalencephaly-Capillary Malformation] - (N=3)	0	(0.0, 70.8)	3 (100)	(29.2, 100.0)
Other - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
Mutation type				
Frequent - (N=23)	12 (52.2)	(30.6, 73.2)	11 (47.8)	(26.8, 69.4)
Less-frequent - (N=9)	0	(0.0, 33.6)	9 (100.0)	(66.4, 100.0)
Lesion type				
Abdominal region - (N=10)	7 (70.0)	(34.8, 93.3)	3 (30.0)	(6.7, 65.2)
Brain - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
Chest - (N=2)	1 (50.0)	(1.3, 98.7)	1 (50.0)	(1.3, 98.7)
Head - (N=5)	0	(0.0, 52.2)	5 (100)	(47.8, 100.0)
Limb - (N=2)	0	(0.0, 84.2)	2 (100)	(15.8, 100.0)
Lower leg - (N=10)	4 (40.0)	(12.2, 73.8)	6 (60.0)	(26.2, 87.8)
Neck - (N=2)	0	(0.0, 84.2)	2 (100)	(15.8, 100.0)
Other - (N=1)	1 (100)	(2.5, 100.0)	0	(0.0, 97.5)
Pelvis - (N=7)	4 (57.1)	(18.4, 90.1)	3 (42.9)	(9.9, 81.6)
Skin - (N=1)	0	(0.0, 97.5)	1 (100)	(2.5, 100.0)
Spinal/paraspinal - (N=2)	1 (50.0)	(1.3, 98.7)	1 (50.0)	(1.3, 98.7)
Upper arm - (N=2)	1 (50.0)	(1.3, 98.7)	1 (50.0)	(1.3, 98.7)
Upper leg - (N=2)	0	(0.0, 84.2)	2 (100)	(15.8, 100.0)
Age (years)				
2-5 - (N=7)	2 (28.6)	(3.7, 71.0)	5 (71.4)	(29.0, 96.3)
6-11 - (N=7)	1 (14.3)	(0.4, 57.9)	6 (85.7)	(42.1, 99.6)
12-17 - (N=9)	4 (44.4)	(13.7, 78.8)	5 (55.6)	(21.2, 86.3)
<18 - (N=23)	7 (30.4)	(13.2, 52.9)	16 (69.6)	(47.1, 86.8)
≥18 - (N=9)	5 (55.6)	(21.2, 86.3)	4 (44.4)	(13.7, 78.8)
Sex				
Male - (N=13)	5 (38.5)	(13.9, 68.4)	8 (61.5)	(31.6, 86.1)
Female - (N=19)	7 (36.8)	(16.3, 61.6)	12 (63.2)	(38.4, 83.7)

- 2-sided 95% Confidence Intervals (CI) are based on the exact (Clopper-Pearson) method.
- The proportion of patients with response defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume if none of the individual target lesions have ≥ 20% increase and in absence of progression of non-target lesions and without new lesions.
- Complete cases are defined as the patients in the efficacy population without a missing response.
- Patients are considered as having a missing response if lesion volume(s) assessment at 24 weeks or 6 months (± 4 weeks) is not available and did not permanently discontinue alpelisib prior to 24 weeks of treatment and did not require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.
- PROS subtypes were grouped as recorded in the eCRF. Patients may have more than one subtype.
Lesion type refers to the anatomical location of the lesion selected by BIRC. Patients may have more than one lesion type.
Source: EPIK-P1 CSR-Table 10-9

A sensitivity analysis based on all patients included in the Efficacy population (N=37), where patients with missing responses (n=5) at Week 24 or 6 months (± 4 weeks) were considered as non-responders, yielded a response rate of 32.4% (12/37 patients; 95% CI: 18.0%, 49.8%). The response rates in

paediatric and adult patients were 26.9% (7/26 patients; 95% CI: 11.6%, 47.8%) and 45.5% (5/11 patients; 95% CI: 16.7%, 76.6%), respectively (Table 24).

Table 26 Sensitivity analyses

Analyses **Criteria**	**n (%)**	**(95% CI)**
Sensitivity analysis 1 (N=37) The missing volumetric assessments at Week 24 were **multiply imputed** for patients with missing response	14 (36.7%)	(20.6, 52.9)
Sensitivity analysis 2 (N=37)		
Best-case scenario: Patients with missing responses at 24 weeks or 6 months (± 4 weeks) were considered as **'responders'**	17 (45.9%)	(29.5, 63.1)
Sensitivity analysis 3 (N=37)		
Worst-case scenario: Patients with missing responses at 24 weeks or 6 months (± 4 weeks) were considered as **'non-responders'**	12 (32.4%)	(18, 49.8)

Source: EPIK-P1 CSR-Table 10-10

5.3.2.2. EPIK-P3 (CBYL719F12401)

Study code	CBYL719F12401
EU CT number	2023-508522-95
NCT number	NCT04980833
Other identifier(s)	EPIK-P3
Location in eCTD	5.3.5.2

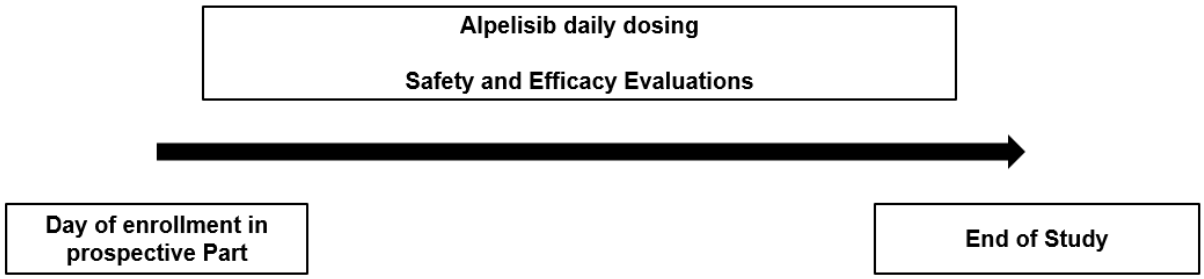
5.3.2.2.1. Study title

A phase II study to evaluate the long-term safety and efficacy of alpelisib in patients with PIK3CA-Related Overgrowth Spectrum (PROS) who previously participated in Study CBYL719F12002 (EPIK-P1).

5.3.2.2.2. Study design

EPIK-P3 is an open label study evaluating the long-term safety and efficacy of alpelisib in patients with PROS who previously participated in EPIK-P1. It consists of two study periods: an initial retrospective (non-interventional) period, which started one day after the EPIK-P1 data cut-off date and lasted up to the initiation of the prospective period and a prospective period in which safety and efficacy data were prospectively collected.

Figure 34: Study design of EPIK-P3 prospective period



Treatment

Alpelisib was administered under fed state (immediately after a meal) at a dose of 50 mg, 125 mg or 200 mg for all patients. Alpelisib tablets were administered orally with food q.d. on a continuous basis.

Patient population

Eligible patients were males and females 2 years of age and older who were previously enrolled in EPIK-P1 and who continued to receive treatment with alpelisib after the data cut-off date for EPIK-P1 (i.e. 09Mar 2020).

5.3.2.2.3. Objectives and estimands

Primary objective

The primary objective was to assess the long-term safety and tolerability of alpelisib over time.

Estimands for the primary objective

Table 27 Estimands for primary objective

Population	**Adults aged ≥18 years and children/adolescents aged 2 to 17 years with PROS (as per the inclusion/exclusion criteria defined in this study).**
Treatment condition	Treatment with daily alpelisib, regardless of dose changes (increase or decrease) or interruptions.
Endpoint (variable)	Incidence of new AEs of Grade ≥ 3 or AEs worsening to Grade ≥ 3 by SOC and PT during the prospective period.
Population-level summary	Proportion of participants with an incidence of a grade ≥3 AE (by system organ class and preferred term) annually. The data will be reported in yearly intervals based on the duration of treatment since starting alpelisib in the MAP/ATU.
Intercurrent events and strategy to handle them	
Intercurrent events	Patients who die or discontinue treatment before the end of study were excluded from the denominator of the yearly interval subsequent to the interval when they discontinued.

The primary scientific question of interest is to assess the effect of alpelisib on the long-term safety and tolerability of participants with PROS as assessed by the frequency of severe AEs (grade ≥3) over time in the prospective period of this study

Statistical methods for estimation and sensitivity analysis on primary estimands

The Safety Set for the prospective period (SAFP) included all patients who received at least one dose of study treatment during the prospective period.

The following age groups were used for specific analyses: 2-5 years; 6-11 years; 12-17 years; < 18 years; ≥ 18 years

No formal statistical power calculations to determine sample size were performed for this study. All patients that were previously enrolled in EPIK-P1 study and treated with at least one dose of alpelisib after the EPIK-P1 data cut-off date were approached for participation in the EPIK P3. All patients who completed the initial retrospective period and were willing to participate in the subsequent prospective period were enrolled. As a result, no formal sample size calculation was performed.

Secondary objectives

Secondary objectives	Endpoints for secondary objective(s)
Retrospective period only: To assess the safety and tolerability of alpelisib	Incidence, type, and severity per common terminology criteria for AEs (CTCAE) v4.03 criteria, causality assessments of AEs, and other safety data including changes in laboratory values, vital signs, and assessment of cardiac function
Prospective period only: To assess the safety and tolerability of alpelisib over time	Incidence, type and severity per CTCAE v4.03 criteria, causality assessments of AEs, and other safety data including changes in laboratory values, vital signs and assessment of cardiac function. Additionally, for this period only, growth, bone/dental development and sexual maturation (for applicable age) will be assessed
Retrospective and prospective period:	
To evaluate the long-term efficacy of alpelisib	Investigator assessment of lesion response as improved, stable, or worsened
To assess symptoms and complications/comorbidities associated with PROS over time	Incidence of PROS-related symptoms and complications/comorbidities among patients with symptoms and complications/comorbidities
To assess the frequency of healthcare visits/hospitalizations due to PROS over time	Number of healthcare visits/hospitalizations due to PROS

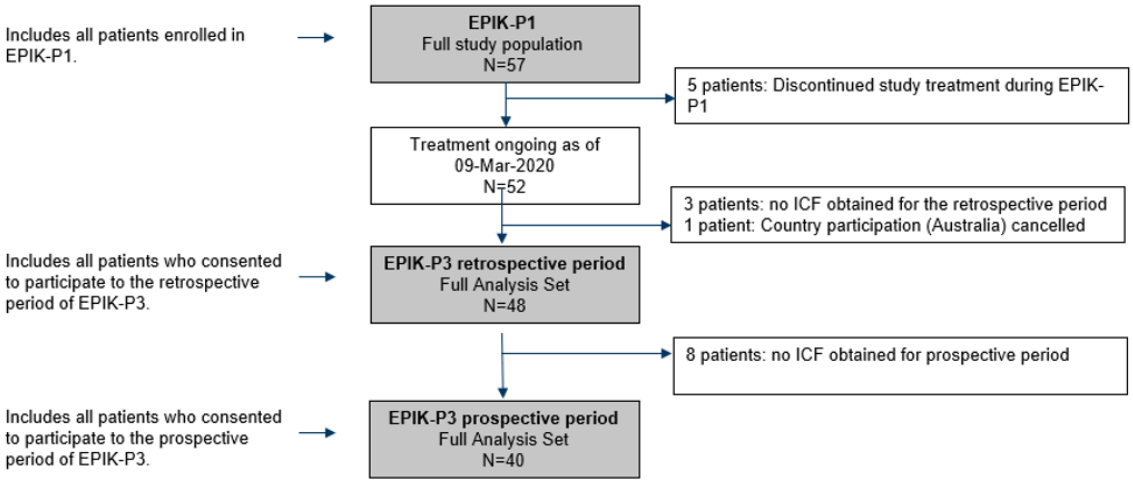
To assess type of medications and non-drug therapies over time	Description of medications and non-drug therapies received: PROS-related treatment(s) other than alpelisib • Medication(s) (e.g., concomitant PROS-related medications including medication for the management of PROS related complications as well as medications to manage complications secondary to alpelisib) • Non-drug treatment(s) (e.g., feeding tube, ketogenic diet, non-invasive device for sleep apnoea, sclerotherapy, endovascular occlusive procedures)' • Alpelisib treatment (e.g., dose, dose adjustments, duration of treatment, dose interruptions, discontinuation) • PROS-related surgeries (e.g., de-bulking or vascular surgery as well as the intended site of the procedure)

5.3.2.2.4. Results

Participant flow and numbers analysed

In total, 48 patients (34 paediatric patients and 14 adult patients) were enrolled in the retrospective period, which is complete. Of those patients, 40 patients (31 paediatric and 9 adult) subsequently enrolled in the prospective period, which is currently ongoing. An overview of the patients enrolled in EPIK-P1 and subsequently in the retrospective and prospective periods of EPIK-P3 is presented in **Figure *35***.

Figure 35: Overview of patients enrolled in EPIK-P1 and subsequently in the retrospective and prospective periods of EPIK-P3



Source: BYLPROS SCE-Figure 1-1

Deviations from study plan

The key changes included modification of the imaging assessment (MRI) frequency and bone age assessment frequency. Moreover, additional instructions for dose escalation and modification for patients treated with 100 mg or 150 mg of alpelisib under the global compassionate use program were provided. Additional instructions for patients not able to swallow alpelisib tablets whole on how to prepare a suspension of alpelisib tablets in water were also provided.

Baseline data.

Demographics:
The median age of the patients at the start of the prospective period was 16.5 years (range: 655 years). Most patients were white (36 [90.0%] patients).

Clinical characteristics:
Medical conditions which were present at the time of the EPIK-P3 retrospective period and ongoing at the start of the prospective period, as well as treatment-emergent AEs from the EPIK-P3 retrospective period that were ongoing at the start of the prospective period, are referred to as 'ongoing medical conditions' for the prospective period.

All enrolled patients (n=40) had at least one ongoing medical condition. The most frequently reported ongoing medical conditions by PT (in ≥ 11 [27.5%] patients) were:

- Vascular malformation: 25 (62.5%) patients
- Limb asymmetry: 21 (52.5%) patients
- Hypertrophy: 13 (32.5%) patients
- Lymphatic malformation: 12 (30.0%) patients
- Lipomatosis, Scoliosis and Lipoma: all in 11 (27.5%) patients

Outcomes and estimation

Overall clinical response
Overall clinical response was assessed by Investigators based on clinical judgement and predefined criteria combination which included clinical evaluation of the patient's general conditions and radiological imaging. The overall clinical response was noted as improved, stable, or worsened, as compared to the previous assessment performed.

The assessment for the overall clinical response of the prospective period was presented by visit (Baseline, Month 12) and by yearly intervals. The yearly interval(s) are based on the duration of treatment since the patient initiated alpelisib in the compassionate use program.

Table 28 Proportion of patients with overall clinical response as assessed by the Investigator during the prospective period by visit and age category (FASP)

Visit	Overall clinical response	Age at the initiation of alpelisib in the compassionate use program					
		2-5 years (N=9) n (%)	6-11 years (N=10) n (%)	12-17 years (N=12) n (%)	Pediatric patients (<18 years) (N=31) n (%)	Adult patients (>=18 years) (N=9) n (%)	All patients (N=40) n (%)
Baseline	Improved	8 (88.9)	7 (70.0)	10 (83.3)	25 (80.6)	8 (88.9)	33 (82.5)
	Stable	1 (11.1)	3 (30.0)	1 (8.3)	5 (16.1)	1 (11.1)	6 (15.0)
	Worsened	0	0	1 (8.3)	1 (3.2)	0	1 (2.5)
12 months*	Improved	3 (33.3)	1 (10.0)	5 (41.7)	9 (29.0)	1 (11.1)	10 (25.0)
	Stable	5 (55.6)	8 (80.0)	7 (58.3)	20 (64.5)	8 (88.9)	28 (70.0)
	Worsened	0	1 (10.0)	0	1 (3.2)	0	1 (2.5)

*Data from 1 patient (F12401- 4902-907) was missing as the MRI for the patient was not performed at the time of the data cut- off for this analysis
Age categories are based on the derived age at the initiation of alpelisib in the compassionate use program.
Each assessment is relative to previous assessment. Baseline assessment is relative to the previous assessment performed during compassionate use program.
Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.

Source: Table 14.2-1.1

Overall lesion response

Overall lesion response was assessed by Investigators based on radiological imaging and, if deemed necessary, other methods of measurement (e.g., circumference measured by rulers) and noted as improved, stable, worsened, or non-evaluable compared to the previous assessment performed.

The overall lesion assessment response (stable, improved, worsened or non-evaluable) based on MRI assessment, was summarized in the same manner as the overall clinical response.

Table 29 Proportion of patients with overall clinical response during the prospective period in yearly interval by age category (FASP)

Yearly interval	Age at the initiation of alpelisib in the compassionate use program						
	Overall clinical response	2-5 years (N=9) n (%)	6-11 years (N=10) n (%)	12-17 years (N=12) n (%)	Pediatric patients (<18 years) (N=31) n (%)	Adult patients (>=18 years) (N=9) n (%)	All patients (N=40) n (%)
2-3 years	Number of patients on treatment (m)	0	2	0	2	2	4
	Improved	0	1 (50.0)	0	1 (50.0)	2 (100)	3 (75.0)
	Stable	0	1 (50.0)	0	1 (50.0)	0	1 (25.0)
3-4 years	Number of patients on treatment (m)	5	6	5	16	7	23
	Improved	4 (80.0)	2 (33.3)	4 (80.0)	10 (62.5)	4 (57.1)	14 (60.9)
	Stable	1 (20.0)	4 (66.7)	1 (20.0)	6 (37.5)	3 (42.9)*	9 (39.1)*
4-5 years	Number of patients on treatment (m)	6	6	7	19	7	26
	Improved	3 (50.0)	2 (33.3)	3 (42.9)	8 (42.1)	0	8 (30.8)
	Stable	3 (50.0)	2 (33.3)	3 (42.9)	8 (42.1)	5 (71.4)*	13 (50.0)*
	Worsened	0	1 (16.7)	1 (14.3)	2 (10.5)	0	2 (7.7)
5-6 years	Number of patients on treatment (m)	5	4	7	16	4	20
	Improved	3 (60.0)	3 (75.0)	6 (85.7)	12 (75.0)	1 (25.0)	13 (65.0)
	Stable	1 (20.0)	1 (25.0)	1 (14.3)	3 (18.8)	0	3 (15.0)
6-7 years	Number of patients on treatment (m)	4	4	6	14	2	16
	Improved	0	0	2 (33.3)	2 (14.3)	1 (50.0)	3 (18.8)
	Stable	1 (25.0)	3 (75.0)	3 (50.0)	7 (50.0)	1 (50.0)	8 (50.0)
7-8 years	Number of patients on treatment (m)	0	0	0	0	1	1
	Improved	0	0	0	0	1 (100)	1 (100)

Age categories are based on the derived age at the initiation of alpelisib in the compassionate use program.
Each assessment is relative to previous assessment. Baseline assessment is relative to the previous assessment performed during compassionate use program.
Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
Number (m) represent the number of patients on treatment in the prospective period at the start of each interval (apart from the first interval). The yearly intervals were based on the duration of treatment since the patient commenced Alpelisib in the compassionate use program. The last assessment within each interval was used for the analysis.
% (n/m) are derived by considering m as denominator.
*Overall clinical response for one patient (F12401-6940-769) was incorrectly captured in 3-4 yearly interval instead of 4-5 yearly interval. The issue is described in Appendix 16.1.14, which also contains the correct data of assessment.
Source: Table 14.2-1.3

Improvement in PROS related signs and symptoms

An improvement in PROS-related signs and symptoms was defined based on at least one grade reduction or resolution of the event. Stabilization in PROS-related signs and symptoms was defined as no change in CTC grade at the 1-year timepoint relative to the start of the prospective period. The most frequently reported (≥ 13 [32.5%] patients) PROS-related signs and symptoms at start of the prospective period were:

- Vascular malformation: 25 (62.5%) patients
- Limb asymmetry: 21 (52.5%) patients
- Hypertrophy: 13 (32.5%) patients

The proportion of patients with improvement and stabilization in the above PROS-related signs and symptoms during the 1-year prospective period relative to the start of the prospective period were:

- Vascular malformation: improvement in 1 (4.0%) patient; stabilization in 24 (96.0%) patients
- Limb asymmetry: stabilization in all 21 (100%) patients
- Hypertrophy: stabilization in all 13 (100%) patients.

During the procedure, the Applicant provided EPIK-P3 3-Year Analysis (data cut-off: 15-JUL-2025). The median duration of exposure to alpelisib during the 3-year prospective period of EPIK-P3 was 39.1 months (range: 17 – 42 months).

Overall clinical response

All patients ongoing in EPIK-P3 at 24 and 36 months had a status of either clinically improved or stable. At 36 months, 67.7% (21/31) of pediatric patients and 55.6% (5/9) of adult patients were improved as compared to the previous assessment, and 29.0% (9/31) of pediatric patients and 44.4% (4/9) of adult patients remained stable. Across the whole 3-year prospective period, 1 patient (2.5%) had worsened overall clinical response, which was reported at the Baseline assessment.

Table 30 Proportion of patients with overall clinical response reported as improved, stable or worsened as assessed by the investigator during the prospective period by visit and by age category (based on age at the initiation of alpelisib in the compassionate use:

Visit	Overall clinical response	2-5 years N=9	6-11 years N=10	12-17 years N=12	Pediatric patients (<18 years) N=31	Adult patients (>=18 years) N=9	All patients N=40
		n (%)					
Baseline	**Improved**	8 (88.9)	7 (70.0)	10 (83.3)	25 (80.6)	8 (88.9)	33 (82.5)
	Stable	1 (11.1)	3 (30.0)	1 (8.3)	5 (16.1)	1 (11.1)	6 (15.0)
	Worsened	0	0	1 (8.3)	1 (3.2)	0	1 (2.5)
12 months	**Improved**	3 (33.3)	1 (10.0)	4 (33.3)	8 (25.8)	1 (11.1)	9 (22.5)
	Stable	6 (66.7)	9 (90.0)	8 (66.7)	23 (74.2)	8 (88.9)	31 (77.5)
24 months	**Improved**	1 (11.1)	2 (20.0)	3 (25.0)	6 (19.4)	3 (33.3)	9 (22.5)
	Stable	8 (88.9)	7 (70.0)	9 (75.0)	24 (77.4)	6 (66.7)	30 (75.0)
36 months	**Improved**	5 (55.6)	7 (70.0)	9 (75.0)	21 (67.7)	5 (55.6)	26 (65.0)
	Stable	4 (44.4)	2 (20.0)	3 (25.0)	9 (29.0)	4 (44.4)	13 (32.5)

Age categories are based on the derived age at the initiation of alpelisib in the compassionate use program. Each assessment is relative to the previous assessment. Baseline assessment is relative to the previous assessment performed during compassionate use program. Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
Source Table: [Appendix 6-Table 14.2-1.1]

Overall lesion assessment

All patients ongoing in EPIK-P3 at 24 and 36 months had a status of either improved or stable. At 36 months, 22.6% (7/31) of pediatric patients and 33.3% (3/9) of adult patients were improved as, and 74.2% (23/31) of pediatric patients and 66.7% (6/9) of adult patients remained stable. Across the whole 3-year prospective period, no patients had worsened overall lesion assessment at any assessment.

Table 31 Proportion of patients with overall lesion assessment reported as improved, stable or worsened as assessed by the investigator during the prospective period by visit and by age category (based on age at the initiation of alpelisib in the compassionate

Visit	Overall clinical response	2-5 years N=9	6-11 years N=10	12-17 years N=12	Pediatric patients (<18 years) N=31	Adult patients (>=18 years) N=9	All patients N=40
		n (%)					
Baseline	**Improved**	8 (88.9)	5 (50.0)	10 (83.3)	23 (74.2)	7 (77.8)	30 (75.0)
	Stable	1 (11.1)	4 (40.0)	2 (16.7)	7 (22.6)	2 (22.2)	9 (22.5)
	Missing	0	1 (10.0)	0	1 (3.2)	0	1 (2.5)
12 months	**Improved**	2 (22.2)	1 (10.0)	4 (33.3)	7 (22.6)	1 (11.1)	8 (20.0)
	Stable	7 (77.8)	9 (90.0)	8 (66.7)	24 (77.4)	8 (88.9)	32 (80.0)
24 months	**Improved**	1 (11.1)	2 (20.0)	2 (16.7)	5 (16.1)	3 (33.3)	8 (20.0)
	Stable	8 (88.9)	7 (70.0)	10 (83.3)	25 (80.6)	6 (66.7)	31 (77.5)
36 months	**Improved**	1 (11.1)	3 (30.0)	3 (25.0)	7 (22.6)	3 (33.3)	10 (25.0)
	Stable	8 (88.9)	6 (60.0)	9 (75.0)	23 (74.2)	6 (66.7)	29 (72.5)

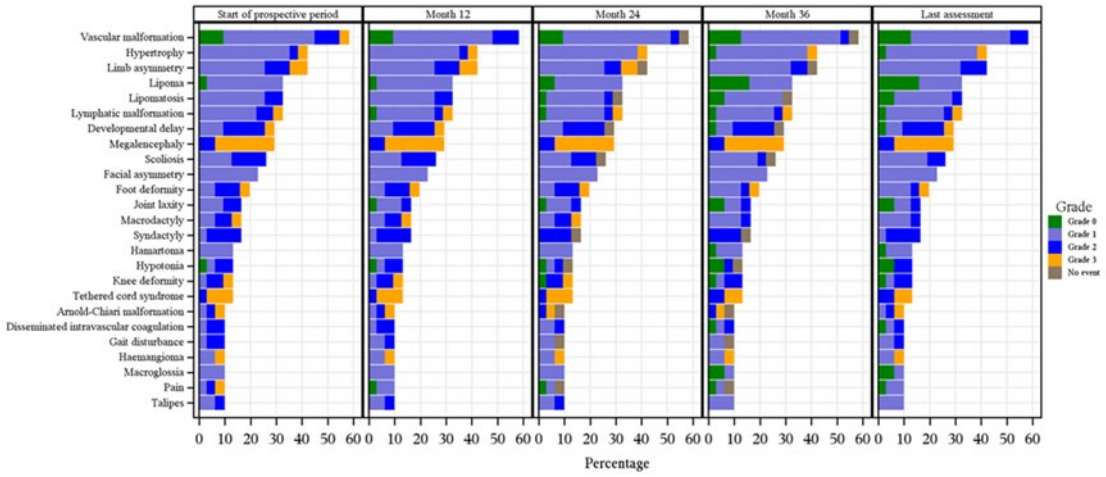
Age categories are based on the derived age at the initiation of alpelisib in the compassionate use program. Each assessment is relative to the previous assessment. Baseline assessment is relative to the previous assessment performed during compassionate use program. Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis. Source Table: [Appendix 6-Table 14.2-1.2]

PROS-related signs and symptoms

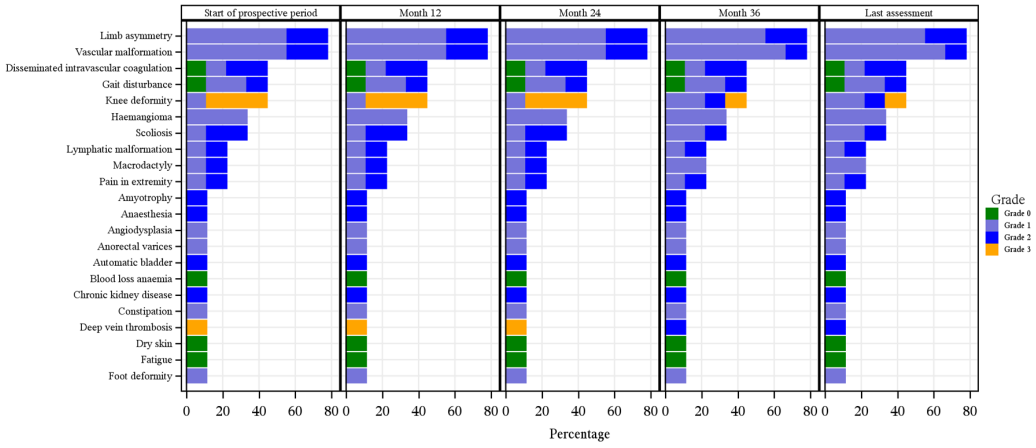
Of the PROS-related signs and symptoms ongoing at the start of the prospective period, improvement (defined as CTC grade reduction or resolution) or stabilisation (defined as no change in CTC grade) was observed by the last assessment prior to the 3-year data cut-off (15-Jul-2025) for almost all reported signs and symptoms. Worsening (defined as an increase in CTC grade) was reported for lymphoedema in 1 pediatric patient and vulvovaginal dryness in 1 adult patient.

Figure 36 Shift in CTCAE grade from start of prospective period for the most frequent PROS-related signs and symptoms by age category (based on age at the initiation of alpelisib in the compassionate use program)

Pediatric patients (<18 years) (N=31)



Adult patients (>=18 years) (N=9)



Age categories are based on the derived age at the initiation of alpelisib in the compassionate use program. The top 20 signs and symptoms are based on the frequency reported in pediatric and adult patients at the start of the prospective period (Day 1). An event is defined as resolved (denoted Grade 0) if there is an end date with no subsequent event prior to the end of the prospective period. Source Figure: [Appendix 6-Figure 14.3-1.1]

PROS-related surgeries

During the 3-year prospective period, 25.8% of pediatric patients (8/31) and 22.2% of adult patients (2/9) had at least one PROS-related surgery. None of the surgeries were considered as rescue surgery.

Each of the 8 pediatric patients had 1 surgery; 50% of these (4/8) were due to disease improvement of PROS as reported by the investigator. One pediatric patient (12.5%), a [2-55]-year-old female at baseline, had an amputation on Day 383 of the prospective period with reason 'scheduled transfemoral amputation at the right lower limb' that had been planned previously. The other 3 surgeries were orthopedic fusion (right femoral epiphysiodesis in the context of leg length inequality), cosmetic surgery (excision of the vascular malformation of the foot) and debulking (surgery performed as a long-term debulking treatment plan) in 1 patient (12.5%) each.

Of the 2 adult patients with surgeries, each had 2 surgeries. One adult patient (50.0%) had two surgeries of liposuction, both due to disease improvement of PROS as reported by the investigator. The other adult patient (50.0%) had a cosmetic surgery due to disease improvement of PROS, and a following surgery with type 'other' due to complication of the cosmetic surgery.

Long-term follow up in EPIK-P3

During the procedure, the Applicant provided MRIs data collected from the retrospective and prospective periods reviewed by the same BRIC process as in EPIK-P1.

The results are based on the totality of PROS lesion evaluations by BIRC from EPIK-P1 to the EPIK-P3 3-year prospective period data (cut-off date of 15-Jul-2025). The analysis is based on the EPIK-P1 efficacy population (37 patients).

Of the 37 patients in the efficacy population, 4 (10.8%) discontinued prior to the EPIK-P1 data cut off date. Of the 33 patients on treatment at the EPIK-P1 cut-off, 31 patients (83.8%) continued into the EPIK-P3 retrospective period. No patient discontinued during the EPIK-P3 retrospective period. Of the patients that participated in the EPIK-P3 retrospective period, 5 patients (13.5%) did not enrol in the prospective period of EPIK-P3. Twenty-six patients (70.3%) continued into the EPIK-P3 prospective period and were ongoing treatment at the time of the 3-year prospective period data cut-off date.

Confirmed response

The proportion of patients in the efficacy population with a confirmed response at any time in the efficacy population was 15/37 (40.5%) (95% CI: 24.8%, 57.9%) as assessed by BIRC.

Table 30 Proportion of patients with confirmed response in the pooling period by age category (Efficacy population)

	2-5 years	6-11 years	12-17 years	Paediatric patients (<18 years)	Adult patients (>=18 years)	All patients
	N=8	N=8	N=10	N=26	N=11	N=37
Confirmed responder: n (%)	3 (37.5)	2 (25.0)	5 (50.0)	10 (38.5)	5 (45.5)	15 (40.5)
Clopper-Pearson (Exact) 95% CI	(8.5, 75.5)	(3.2, 65.1)	(18.7, 81.3)	(20.2, 59.4)	(16.7, 76.6)	(24.8, 57.9)

A responder is defined by achieving a >= 20% reduction from index date in the sum of target lesion volumes (by BIRC), provided that none of the individual target lesions have >= 20% increase from index date or nadir and in absence of progression of non-target lesions and without new lesions. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of response. Patients who permanently discontinue alpelisib prior to confirmation of response and patients who received surgery as rescue therapy prior to confirmation of response are considered non-responders.

Source: [Appendix 2: Table 14.2-1.1_exp]

Duration of response (DoR)

The end of response was defined as the date of first documented disease progression, rescue surgery or death due to any cause. Due to the low number of progressions observed, the median duration of response was not evaluable.

Three of 15 patients (20%) with a confirmed response had progression. All three progressions were due to increase in volume of target lesion ≥20% from nadir; All three patients were still ongoing treatment at the 3-year prospective period data cut-off.

5.3.2.3. EPIK-P2

Study code	CBYL719F12201
EU CT number	2023-508530-34
NCT number	NCT04589650
Other identifier(s)	EPIK-P2
Location in eCTD	5.3.5.1

5.3.2.3.1. Study title

A Phase II double-blind study with an upfront, 16-week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA related overgrowth spectrum (PROS).

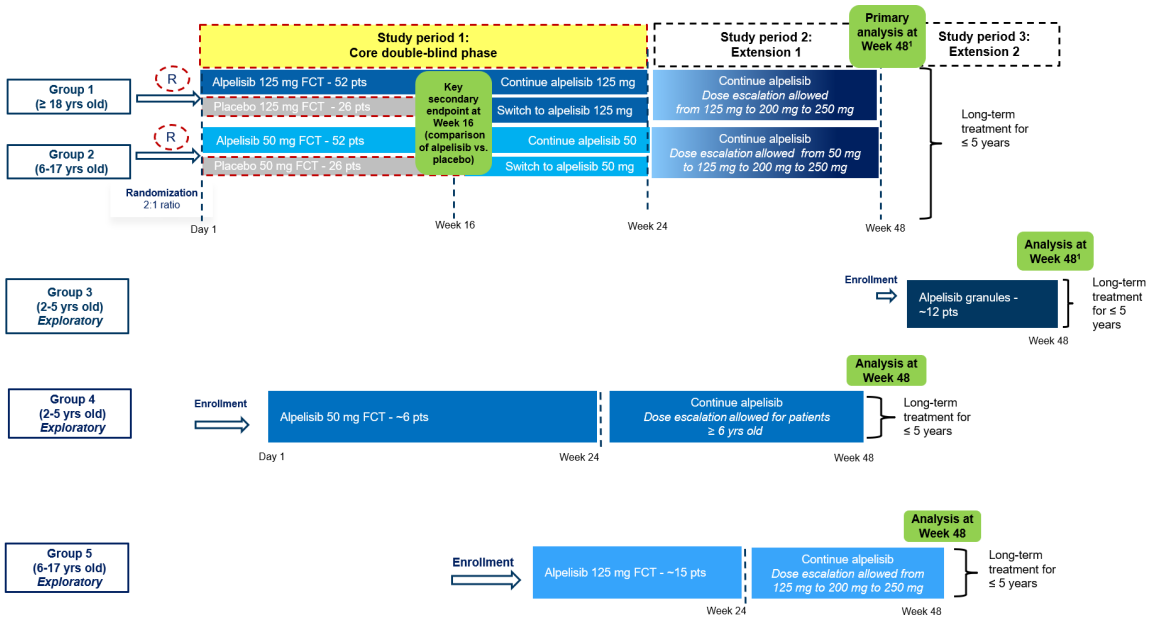
5.3.2.3.2. Study design

EPIK-P2 is an ongoing Phase II multi-centre trial with an initial 16-week, randomized, double-blind, placebo-controlled period, followed by two extension periods in paediatric and adult patients with PROS. The following 5 groups were to be assessed in the study:

- Group 1 (adult patients)
- Group 2 (paediatric patients 6 to 17 years old)
- Group 3 (paediatric patients 2 to 5 years old)
- Group 4 (paediatric patients 2 to 5 years old)
- Group 5 (paediatric patients 6 to 17 years old)

Exploratory groups 3 (2 to 5 years old) and 4 (2 to 5 years old) were included in the study to further explore the efficacy and safety in paediatric patients. Group 5 was included in the study to assess a starting dose of alpelisib 125 mg in paediatric patients 6 to 17 years of age.

Figure 37: Study schema



[1] Study level milestones once all patients had completed the specified time point or discontinued earlier.
Source: BYL719 PROS SCE-Figure 1-4

Treatment

Study treatment in Group 1 and Group 2

Eligible patients entered the study and started treatment with alpelisib/matching placebo at 125 mg q.d. p.o. in Group 1 or 50 mg alpelisib/matching placebo q.d. p.o. in Group 2. Both groups were enrolled in the study in parallel.

In the Core Period 1, patients received treatment in a blinded fashion, with an upfront 16 weeks placebo-controlled period. After Week 16, those patients who were randomized to receive placebo were switched to active treatment with alpelisib 125 mg q.d. p.o (Group 1) or 50 mg q.d. p.o (Group 2). Those patients who were randomized to receive alpelisib continued their treatment at the same dose level.

If the dose of alpelisib/matching placebo was reduced during the initial 16 weeks of treatment because of safety/tolerability concerns, the patients were to continue their treatment at the reduced dose.

During the initial 16 weeks of the Core period, study treatment was given in a blinded fashion, followed by an open-label fashion starting from Week 17 of the Core period. Treatment assignment to the treatment arms remained blinded to patients, investigators, and the study team until the time of the primary analysis, when the last patient reached Week 48 from randomization or discontinued earlier.

Study treatment in Group 4

Patients in Group 4 received alpelisib FCT 50 mg q.d. in an open-label setting.

Study treatment in Group 5

Patients in Group 5 received alpelisib FCT 125 mg q.d. in an open-label setting.

Randomisation

Groups 1 (⩾ 18 years of age) and 2 (6 to 17 years of age)

The CTT remained blinded to the identity of the randomized treatment assignment in Groups 1 and 2 from the time of randomization until analysis of the primary endpoint.

Groups 3, 4, and 5

Treatment was open.

Patient population

Main inclusion criteria

Male or female patients age ≥ 2 years with diagnosis of PROS and documented evidence of a somatic mutation(s) in the PIK3CA gene with symptomatic and /or progressive overgrowth and at least one measurable PROS-related lesion confirmed by BIRC assessment who had syndromic disease or isolated features

Adequate bone marrow and organ function as assessed by central laboratory for eligibility.

Presence of at least one PROS-related measurable lesion defined as a lesion with longest diameter ≥ 2 cm, when the volume could be accurately and reproducibly measured by MRI, and associated with complaints, clinical symptoms or functional limitations affecting the patient's everyday life. Measurability was confirmed by BIRC before randomization.

Exclusion criteria

- Patient with only isolated macrodactyly, epidermal nevus/nevi and macroencephaly (the only clinical feature or a combination of any three of them), in absence of other PROS-related lesions at the time of informed consent.
- Previous treatment with alpelisib and/or any other PI3K inhibitor(s).
- Radiation exposure for PROS treatment purpose within the previous 12 months
- Debulking or other major surgery performed within 3 months.
- Clinically meaningful bleeding related to PROS within 28 days before study treatment start, clinically meaningful PROS-related thrombotic event within 30 days before informed consent, and/or sclerotherapy/embolization for vascular complications performed within 6 weeks before informed consent.
- Clinically significant heart disease at time of informed consent.
- Patients with an established diagnosis of type I diabetes mellitus or uncontrolled type II diabetes mellitus at time of informed consent.
- Known history of seizure, or epilepsy, regardless of relatedness to PROS spectrum at time of informed consent, when epilepsy was not controlled and/or the patient may not be switched to non-enzyme inducing antiepileptic drug(s) at time of informed consent.

5.3.2.3.3. Objectives and estimands

Primary objective

Table 32 Primary objective and related endpoint

Primary objective	Endpoint for primary objective

• To demonstrate the efficacy of alpelisib as measured by the proportion of patients randomized to alpelisib with a confirmed objective response (by blinded independent review committee (BIRC)) in at least one of the following groups:
  • Group 1 (≥ 18 years)
  • Group 2 (6 – 17 years)
	• Response (yes/no) defined by achieving at least 20% reduction from baseline in the sum of target lesion volumes (1 to 3 lesions, assessed by MRI by a (BIRC)), provided that none of the individual target lesions has ≥ 20% increase from baseline and in absence of progression of non-target lesions and without new lesions. Confirmation of response requires a subsequent imaging assessment performed at least 4 weeks after the onset of the response.

Estimands for the primary objective

The primary scientific question of interest for children/adolescents aged 6 to 17 years (in Group 2) and adults (Group 1: ≥ 18 years) with PROS was to assess the benefit of alpelisib with regards to the proportion of confirmed responders by BIRC, considering patients who discontinue treatment prior to confirmation of response and patients who received surgery as rescue therapy for any PROS lesions prior to confirmation of response as non-responders.

The primary estimands were characterized by the following 5 attributes:

1. Treatment: The randomized treatment with daily alpelisib, regardless of dose changes, in the absence of rescue surgery for PROS lesions.
2. Population: Children/adolescents aged 6 to 17 years and adults aged ≥ 18 years with PROS (as per the inclusion/exclusion criteria).
3. Intercurrent events:

- Patients discontinuing treatment prior to confirmation of response: Classified as a non-responder.
- Patients receiving surgery as rescue therapy for any PROS lesions (target or other) prior to confirmation of response: Classified as a non-responder.

4. Variable: response (yes/no) defined by achieving ≥ 20% reduction from baseline in the sum of target lesion volumes (1 to 3 lesions, assessed by MRI by BIRC), provided that none of the individual target lesions had a ≥ 20% increase from baseline and in the absence of progression of non-target lesions and without new lesions. Confirmation of response required a subsequent imaging assessment to be performed at least 4 weeks after the onset of the response.
5. Summary measure: Proportion of patients (children/adolescents aged 6-17 years and adults) with confirmed objective response (by BIRC).

Statistical methods for estimation and sensitivity analysis on primary estimands

Primary efficacy endpoint was the proportion of patients with confirmed response in group 2 patients. A confirmed response rate of 15% or less would be considered "as insufficient" level of efficacy. The response rate accuracy was calculated using the 97.5% one-sided exact confidence limit and the response rate point-estimate was tested versus the lower acceptable limit (15%) using an exact binomial test.

No sensitivity analyses were performed due to the failure to achieving the primary objective.

Secondary objectives

Secondary objectives	Endpoints for secondary objectives
Key secondary objective	**Endpoint for key secondary objective**
• To demonstrate the efficacy of alpelisib vs placebo based on the comparison of the proportion of patients with response at Week 16 in Group 1 or Group 2	Response (yes/no) at Week 16 (by BIRC).
Other secondary objectives	**Endpoints for other secondary objectives**
To assess the efficacy of alpelisib as measured by the proportion of patients with a response at Week 24 (by BIRC) in Group 1 and Group 2	Response (yes/no) at Week 24 (by BIRC).
• To assess safety and tolerability of alpelisib as compared to placebo in Group 1 and Group 2 up to Week 16	• Incidence, type, and severity of treatment-emergent adverse events per CTCAE v4.03 criteria and other safety data including changes in laboratory values, vital signs, assessments of cardiac and lung functions.
• To assess the overall safety and tolerability of alpelisib in patients with PROS over time	• Incidence, type and severity of treatment-emergent adverse events per CTCAE v4.03 criteria and other safety data including changes in laboratory values, vital signs, assessments of cardiac and lung functions, growth, bone/dental development and sexual maturation (for applicable age).
• To assess changes in patient-reported pain intensity and overall severity of symptoms at Week 16 on treatment with alpelisib as compared to placebo in paediatric and adult populations	• Change from baseline to Week 16 in Brief Pain Inventory (BPI) Worst Pain Intensity Item of the Patient Reported Outcomes (PRO) diary and Patient Global Impression of Symptom Severity in paediatric (12 to17 yr old) and adult populations (≥ 18 yr-old).

Secondary objectives	Endpoints for secondary objectives

• To assess changes in target and non-target lesions over time and appearance of new lesions on treatment from baseline over time	• Change from baseline (as assessed by BIRC) in the:
	  • Sum of target lesion volume
	  • Sum of MRI-measurable non-target lesion volume
	  • Sum of all MRI-measurable (target and non-target) lesion volume
	• Change in other non-target lesions (by BIRC)
	• Appearance of new lesions (by BIRC).

• To assess the PK of alpelisib in adult and paediatric patients with PROS	• PK parameters (e.g., Cmax, Ctrough) in Group 1 and Group 2.
• To assess changes in patient-reported pain, health-related quality of life and overall impression of symptoms in paediatric and adult populations over time	• Change in scores from BPI items, or Wong-Baker Faces Scale (age appropriate), Patient Reported Outcome Measurement Information System (PROMIS) profile and Patient Global Impression of Symptom Severity.
• To assess the duration of response in patients who receive alpelisib	• Duration of response in patients who receive alpelisib and who satisfy the response criteria (by BIRC).
• To assess the time to treatment failure in patients who are on treatment with alpelisib	• Time to treatment failure in patients who are on treatment with alpelisib.
• To assess the rate of overall clinical response as assessed by Investigator at the scheduled protocol visits for disease evaluation (e.g., Week 16, 24, 40, 48, 72, 96 and thereafter every 48 weeks)	• Overall clinical response as assessed by Investigator.
• To assess the proportion of patients with a response at the scheduled protocol visits for disease evaluation during the extension periods.	• Response (yes/no) at scheduled protocol visit.
• To assess changes in symptoms and complications/comorbidities up to Week 16 on treatment with alpelisib as compared to placebo.	• Change in PROS-related symptoms and complications/comorbidities up to Week 16 among patients with symptoms and complications/comorbidities present at baseline.
• To assess changes in symptoms and complications/ comorbidities associated with PROS over time	• Change in PROS-related symptoms and complications/comorbidities among patients with symptoms and complications/comorbidities present at baseline.
• To assess the frequency of healthcare visits/hospitalizations due to PROS, rescue surgeries for PROS (incl. avoidance/delay in planned disease-related surgery) over time	• Number/percentage of patients with healthcare visits/hospitalized due to PROS; number of hospitalizations. • Number/percentage of patients with surgeries required to manage PROS; number of surgeries.

Estimands for the secondary objectives

The key secondary scientific question of interest for children/adolescents aged 6 to 17 years (in Group 2) and adults (Group 1: ≥ 18 years) with PROS was to assess the benefit of alpelisib as compared to placebo with regards to the proportion of responders at Week 16, considering patients who discontinued

treatment prior to Week 16 and patients who received surgery as rescue therapy for any PROS lesions as non-responders.

The key secondary estimands were characterized by the following 5 attributes:

1. Treatment: the randomized treatment (daily alpelisib or placebo), regardless of dose changes, in the absence of rescue surgery for PROS lesions.
2. Population: Children/adolescents aged 6 to 17 years and adults aged ≥ 18 years with PROS (as per the inclusion/exclusion criteria).
3. Intercurrent events:
   - Patients discontinuing treatment prior to Week 16: Classified as a non-responder.
   - Patients receiving surgery as rescue therapy for any PROS lesions (target or other) prior to Week 16: Classified as a non-responder.
4. Variable: response (yes/no) defined by achieving a ≥ 20% reduction from baseline in the sum of target lesion volumes (1 to 3 lesions, by BIRC) at Week 16, provided that none of the individual target lesions had ≥ 20% increase from baseline at Week 16 and in the absence of progression of non-target lesions and without new lesions.
5. Summary measure: Difference in proportion of patients (children/adolescents aged 6-17 years and adults) who achieved a response at Week 16.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

For the key secondary objective, it was assumed that the response rate at Week 16 was 30% with alpelisib and 5% with placebo. Patients were randomized in the two treatment arms in a 2:1 ratio to detect a 25% difference in response rate with 61.7% power using Fisher's exact test and one-sided α = 1.25%. Given the hierarchical testing strategy between the primary and the key secondary endpoint, this power was conditional on the primary endpoint being met in the respective age group.

5.3.2.3.4. Results

Participant flow and numbers analysed

Overall, 231 patients with PROS were screened in this study from 35 centres in 12 countries. Of these, 41 patients were screen failures, and 2 patients discontinued per subject/guardian decision from the study during screening.

The data is presented for the primary analysis corresponding to a DCO date of 20-Mar-2024 when all patients from Groups 1 and 2 had been treated for at least 48 weeks or discontinued earlier.

Table 33 Patient disposition in Groups 1 and 2 (FAS)

Disposition Reason	Group 1 (≥ 18yrs) Alpelisib N=54 n (%)	Placebo N=27 n (%)	All adults N=81 n (%)	Group 2 (6 - 17yrs) Alpelisib N=56 n (%)	Placebo N=28 n (%)	All pediatrics N=84 n (%)
Patients randomized	54 (100)	27 (100)	81 (100)	56 (100)	28 (100)	84 (100)
Treated	54 (100)	27 (100)	81 (100)	56 (100)	28 (100)	84 (100)
Summary of patients treated						
Treatment ongoing in Extension 2 (> weeks 48) #	42 (77.8)	23 (85.2)	65 (80.2)	53 (94.6)	25 (89.3)	78 (92.9)
Discontinued during Core (weeks 1-16)	2 (3.7)	1 (3.7)	3 (3.7)	0	2 (7.1)	2 (2.4)
Discontinued during Core (weeks 17-24)	0	0	0	1 (1.8)	0	1 (1.2)
Discontinued during Extension 1 (weeks 25-48)	6 (11.1)	2 (7.4)	8 (9.9)	0	0	0
Discontinued during Extension 2 (> weeks 48)	4 (7.4)	1 (3.7)	5 (6.2)	2 (3.6)	1 (3.6)	3 (3.6)
Completed Core *	52 (96.3)	26 (96.3)	78 (96.3)	55 (98.2)	26 (92.9)	81 (96.4)
Completed Extension 1 *	46 (85.2)	24 (88.9)	70 (86.4)	55 (98.2)	26 (92.9)	81 (96.4)
Discontinued at anytime	12 (22.2)	4 (14.8)	16 (19.8)	3 (5.4)	3 (10.7)	6 (7.1)
Reason for discontinuation						
Subject decision	6 (11.1)	2 (7.4)	8 (9.9)	2 (3.6)	0	2 (2.4)
Adverse event	3 (5.6)	1 (3.7)	4 (4.9)	1 (1.8)	1 (3.6)	2 (2.4)
Physician decision	1 (1.9)	1 (3.7)	2 (2.5)	0	0	0
Unsatisfactory therapeutic effect	2 (3.7)	0	2 (2.5)	0	0	0
Death	0	0	0	0	1 (3.6)	1 (1.2)
Guardian decision	0	0	0	0	1 (3.6)	1 (1.2)
Discontinued prior to Week 17	2 (3.7)	1 (3.7)	3 (3.7)	0	2 (7.1)	2 (2.4)
Reason for discontinuation prior to Week 17						
Subject decision	1 (1.9)	1 (3.7)	2 (2.5)	0	0	0
Adverse event	1 (1.9)	0	1 (1.2)	0	0	0
Death	0	0	0	0	1 (3.6)	1 (1.2)
Guardian decision	0	0	0	0	1 (3.6)	1 (1.2)
Discontinued at or prior to Week 24 but after Week 16	0	0	0	1 (1.8)	0	1 (1.2)
Reason for discontinuation at or prior to Week 24 but after Week 16						
Subject decision	0	0	0	1 (1.8)	0	1 (1.2)
Discontinued during Extension 1	6 (11.1)	2 (7.4)	8 (9.9)	0	0	0
Reason for discontinuation during Extension 1						
Subject decision	2 (3.7)	1 (3.7)	3 (3.7)	0	0	0
Adverse event	2 (3.7)	0	2 (2.5)	0	0	0
Physician decision	1 (1.9)	1 (3.7)	2 (2.5)	0	0	0
Unsatisfactory therapeutic effect	1 (1.9)	0	1 (1.2)	0	0	0
Discontinued during Extension 2	4 (7.4)	1 (3.7)	5 (6.2)	2 (3.6)	1 (3.6)	3 (3.6)
Reason for discontinuation during Extension 2						
Subject decision	3 (5.6)	0	3 (3.7)	1 (1.8)	0	1 (1.2)
Adverse event	0	1 (3.7)	1 (1.2)	1 (1.8)	1 (3.6)	2 (2.4)
Unsatisfactory therapeutic effect	1 (1.9)	0	1 (1.2)	0	0	0

Ongoing at the time of the data cut-off date 20 MAR 2024.
* Patients are either ongoing on treatment or have discontinued from the study.
Patients who completed a study period (i.e., Core, Extension 1) are continuing into the next study period.

Table 34 Patient disposition in the exploratory groups (FAS)

Disposition	Group 4 (2 - 5yrs) All pediatrics N=7 n (%)	Group 5 (6 - 17yrs) All pediatrics N=16 n (%)
Patients treated	7 (100)	16 (100)
Summary of patients treated		
Treatment ongoing in Core (weeks 17-24) #	0	2 (12.5)
Treatment ongoing in Extension 1 (weeks 25-48) #	0	9 (56.3)
Treatment ongoing in Extension 2 (> weeks 48) #	7 (100)	4 (25.0)
Discontinued during Core (weeks 1-16)	0	1 (6.3)
Completed Core *	7 (100)	13 (81.3)
Completed Extension 1 *	7 (100)	4 (25.0)
Discontinued at anytime	0	1 (6.3)
Reason for discontinuation		
Adverse event	0	1 (6.3)
Discontinued at or prior to Week 17	0	1 (6.3)
Reason for discontinuation at or prior to Week 17		

Ongoing at the time of the data cut-off date 20 Mar 2024.
* Patients are either ongoing on treatment or have discontinued from the study.
Patients who completed a study period (i.e., Core, Extension 1) are continuing into the next study period.
Source: Table 14.1-1.3c

Deviations from study plan

All the protocol amendments described below (Table 34) occurred prior to database lock/unblinding for the EPIK-P2 primary analysis.

Table 35 Summary of key protocol amendments

Amendment number and date	Summary of key changes
Amendment 1 14-Jan-2022	At the time of the release of this Global Protocol Amendment, 24 sites had been initiated, 11 participants were in screening and 43 had been randomized. • Updated the elements of the study design based on the results from Study [CBYL719F12002] (entitled "Retrospective chart review study of adult or paediatric patients ≥ 2 years of age, with severe or life|-threatening PIK3CA-Related Overgrowth Spectrum (PROS), who have received alpelisib as part of a compassionate use program"). This specifically concerns the hypothesis to be tested for the primary endpoint, the sample size and the addition of a secondary objective to assess the "Time to Treatment Failure". • Included an exploratory group (i.e., Group 4) of approximately 6 patients, 2 to 5 years of age, treated with 50 mg alpelisib film-coated tablets. • Adapted the global study protocol to the changes requested by HAs/ECs/IRBs or other regulatory institutions, that were already implemented through local protocol amendments in Germany, the United Kingdom (UK) and China. • Modified the imaging assessment (MRI and photography) frequency of Groups 1 and 2, added a new imaging assessments frequency for Group 4,

Amendment number and date	Summary of key changes

	and clarified the timing of the mandatory unscheduled MRI following a suspected disease progression.
	• Revised several eligibility criteria:
	  • Updated Inclusion criteria to:
	  • Clarify that in case archival tissue is not available, collection of a fresh tissue biopsy is required for patients in Groups 1 and 2, if it is not clinically contraindicated.
	  • Indicate that fresh tissue biopsy is not mandatory for patients in Groups 3 and 4.
	  • Included criteria specific to patients in Germany and China based on local requirements.
	  • Modified Inclusion criteria to clarify that INR must be ≤1.5 unless anticoagulant therapy (related to PROS) is ongoing at the time of screening and added note to clarify that patients receiving anticoagulants for PROS related coagulopathy, primary or secondary prophylaxis of thrombosis may be included in the study.
	  • Updated the note to Exclusion criteria to clarify the washout-period for patients previously treated with small molecules (such as mTOR inhibitors, AKT inhibitors) and/or anti angiogenic agents for PROS.
	  • Revised Exclusion criteria to make an exception for Groups 3 and 4 (inclusive of patients 2-5 years of age) for whom spirometry is not applicable; criteria additionally revised to remove the language "(after clarification with Novartis)" and to clarify that when lung function impairment is, in the opinion of the investigator, related to PROS the patient may be included but that caution must be exercised.
	  • Updated Exclusion criteria in response to the Food and Drug Administration (FDA): modified to allow for enrolment of patients with a known history of Human Immunodeficiency Virus (HIV) infection.
	• Added language related to public health emergency (when it limits or prevents on-site study visits during a public health emergency, such as a pandemic).

Amendment 2 28-Sep-2022	At the time of the release of this Global Protocol Amendment, 37 sites had been initiated, and 110 participants had been randomized/enrolled (47 in Group 1 [≥18 years]; 58 in Group 2 [6-17 years] and 5 in Group 4 [2-5 years). • Modified the primary objective and related endpoint from a response at Week 24 to a confirmed objective response by a blinded independent review committee (BIRC). • Added a secondary objective and related endpoint to reflect the response at Week 24 (by BIRC). • Included an additional analysis to characterize the durability of confirmed objective response at the time that patients from Groups 1 (≥18 years), 2 (6-17 years), 4 (2-5 years) and 5 (6-17 years) have reached at least 42 months (i.e., 36 months after the Week 24 time-point) of treatment or discontinued earlier to characterize the duration of response (DOR). • Included an exploratory group (i.e., Group 5) of approximately 15 patients, 6 to 17 years of age, treated with a starting dose of 125 mg alpelisib film-coated tablets. • Updated imaging assessment (whole-body MRI and photography) frequency for Groups 1, 2, 4 and 5 by adding a new imaging assessment at Week 72. • Clarification provided on the whole-body MRI requirement and the timing of the mandatory unscheduled whole-body MRI prior to a surgery due to PROS. • Revision added to specify Walking Distance Test is not applicable for Groups 3 and 4 patients (2-5 years of age).

Amendment number and date	Summary of key changes
Amendment 3 11-Apr-2023	At the time of the release of this Global Protocol Amendment, 39 sites had been initiated and 177 participants had been either randomized or enrolled (81 in Group 1 [≥18 years of age]; 84 in Group 2 [6-17 years of age]; 7 in Group 4 [2-5 years of age] and 5 in Group 5 [6-17 years of age]). • Added a new exclusion criterion: Patients with clinically significant worsening of PROS-related laboratory anomalies, physical signs and symptoms (such as, but not limited to increase of D-dimers, worsening of underlying pain, newly occurring swelling or redness) indicating an uncontrolled condition during the screening phase, particularly if systemic treatment with any other inhibitor of the PI3K/AKT/mTOR pathway was stopped prior to the start of study treatment. This includes but is not limited to hypercoagulability state in patients not receiving prophylactic treatment. • Added a mandate for a physical examination on Day 1 of the trial, prior to the start of study treatment. • Included the event of colitis and guidance to consider additional treatment for the management of colitis.
Amendment 4 05-Oct-2023	At the time of the release of this Global Protocol Amendment, 186 participants had been either randomized or enrolled in EPIK-P2 (81 in Group 1 [≥ 18 years of age]; 84 in Group 2 [6-17 years of age]; 7 in Group 4 [2-5 years of age] and 14 in Group 5 [6-17 years]). Enrolment in Groups 1, 2, and 4 had been completed • The protocol amendment was done to change the timing of the primary analysis to occur after all ongoing patients from Groups 1 and 2 have completed at least 48 weeks (instead of at least 24 weeks) of treatment or discontinued earlier. • In line with the change in the timing of the primary analysis, the durability of the confirmed objective response was planned to be assessed when all patients from Groups 1 and 2 had reached at least 48 months (instead of at least 42 months) of treatment or discontinued earlier to characterize the duration of response (DOR).

Source: EPIK-P2 Primary analysis CSR-Section 9.8.1

Baseline data

Patient demographics and baseline characteristics by treatment are presented below.

Table 36 Patient demographics in Groups 1 and 2 (FAS)

Characteristic Categories/Statistics	Group 1 (≥ 18yrs) Alpelisib N=54	Placebo N=27	All adults N=81	Group 2 (6 - 17yrs) Alpelisib N=56	Placebo N=28	All pediatrics N=84
Age category - n (%)						
Children, 6 - <12 years	NA	NA	NA	28 (50.0)	19 (67.9)	47 (56.0)
Adolescent, 12 - <18 years	NA	NA	NA	28 (50.0)	9 (32.1)	37 (44.0)
18 - <65 years	54 (100)	27 (100)	81 (100)	NA	NA	NA
Age (years)						
n	54	27	81	56	28	84
Mean (SD)	31.9 (9.61)	30.8 (12.24)	31.6 (10.49)	10.9 (3.56)	9.9 (3.29)	10.6 (3.49)
Median	31.5	27.0	31.0	11.5	9.0	10.0
Q1-Q3	23.0-39.0	20.0-35.0	22.0-39.0	8.0-14.0	7.0-12.0	8.0-14.0
Min-Max	18-58	18-62	18-62	6-17	6-17	6-17
Sex - n (%)						
Male	20 (37.0)	13 (48.1)	33 (40.7)	29 (51.8)	16 (57.1)	45 (53.6)
Female	34 (63.0)	14 (51.9)	48 (59.3)	27 (48.2)	12 (42.9)	39 (46.4)
Race - n (%)						
White	48 (88.9)	22 (81.5)	70 (86.4)	42 (75.0)	25 (89.3)	67 (79.8)
Asian	6 (11.1)	3 (11.1)	9 (11.1)	10 (17.9)	3 (10.7)	13 (15.5)
More than one race	0	1 (3.7)	1 (1.2)	2 (3.6)	0	2 (2.4)
Black or African American	0	1 (3.7)	1 (1.2)	1 (1.8)	0	1 (1.2)
Unknown	0	0	0	1 (1.8)	0	1 (1.2)
Ethnicity - n (%)						
Not Hispanic or Latino	51 (94.4)	25 (92.6)	76 (93.8)	47 (83.9)	22 (78.6)	69 (82.1)
Hispanic or Latino	3 (5.6)	1 (3.7)	4 (4.9)	6 (10.7)	6 (21.4)	12 (14.3)
Unknown	0	1 (3.7)	1 (1.2)	2 (3.6)	0	2 (2.4)
Not reported	0	0	0	1 (1.8)	0	1 (1.2)
BMI (kg/m²)						
n	53	27	80	55	28	83
Mean (SD)	27.4 (8.71)	27.5 (6.77)	27.4 (8.06)	20.5 (4.32)	17.7 (2.92)	19.6 (4.11)
Median	26.0	26.4	26.2	20.0	17.8	18.9
Q1-Q3	22.2-30.8	22.1-31.7	22.1-31.4	17.3-23.8	15.5-19.0	16.5-22.6
Min-Max	17.5-70.5	18.5-46.5	17.5-70.5	13.7-32.3	13.5-26.8	13.5-32.3
Missing	1	0	1	1	0	1

Table 37 Patient demographics in the exploratory groups 4 and 5 (FAS)

Characteristic Categories/Statistics	Group 4 (2 - 5yrs) All pediatrics N=7	Group 5 (6 - 17yrs) All pediatrics N=16
Age category - n (%)		
Children, 2 - <6 years	7 (100)	NA
Children, 6 - <12 years	NA	12 (75.0)
Adolescent, 12 - <18 years	NA	4 (25.0)
Age (years)		
n	7	16
Mean (SD)	3.3 (1.11)	9.8 (3.75)
Median	3.0	9.0
Q1-Q3	2.0-4.0	7.0-12.0
Min-Max	2-5	6-17
Sex - n (%)		
Male	4 (57.1)	8 (50.0)
Female	3 (42.9)	8 (50.0)
Race - n (%)		
White	7 (100)	13 (81.3)
Asian	0	2 (12.5)
Unknown	0	1 (6.3)
Ethnicity - n (%)		
Not Hispanic or Latino	7 (100)	13 (81.3)
Hispanic or Latino	0	3 (18.8)
BMI (kg/m²)		
N	7	16
Mean (SD)	17.69 (2.549)	19.20 (5.139)
Median	17.00	17.99
Q1-Q3	15.63-19.94	15.50-20.91
Min-Max	15.2-22.3	14.0-33.0

Outcomes and estimation

Primary efficacy results

Primary efficacy endpoint was the proportion of patients with confirmed response. A confirmed response rate of 15% or less has been considered "as insufficient" level of efficacy.

The study did not meet its primary objective in either Group 1 (adult patients starting at a dose of 125 mg) or Group 2 (paediatric patients 6 to 17 years of age starting at a dose of 50 mg).

Table 38 Proportion of patients with confirmed objective response (FAS)

	Group 1 (≥ 18yrs) Alpelisib N=54	Group 2 (6 - 17yrs) Alpelisib N=56
Responder: n (%)	9 (16.7)	13 (23.2)
Clopper-Pearson (Exact) 97.5% CI	(7.0, 31.1)	(11.9, 38.3)
Clopper-Pearson (Exact) 95% CI	(7.9, 29.3)	(13.0, 36.4)
Adjusted p-value for H0: RR ≤ 0.15 vs H1: RR > 0.15 [1]	0.4223	0.1364

RR: Confirmed response rate.
[1] Adjusted p-values obtained from the multiple testing procedure.
* Indicates statistical significance (1-sided) at the 0.025 level.

Secondary efficacy results

As the primary objective was not met, the key secondary endpoint was not statistically tested.

Key secondary efficacy analyses: Proportion of patients with response at Week 16

At Week 16, responses were observed in the alpelisib arm, and no responses were seen in the placebo arm.

Table 39 Proportion of patients with response at Week 16 (FAS)

			Between treatment comparison		
Treatment	Responder/N (%)	95% CI [1]	Comparison	Difference	95% CI [2]
Group 1 (≥ 18yrs)					
Alpelisib	6/54 (11.1)	(4.2, 22.6)	vs Placebo	11.1	(-12.9, 34.3)
Placebo	0/27	(0.0, 12.8)			
Group 2 (6 - 17yrs)					
Alpelisib	5/56 (8.9)	(3.0, 19.6)	vs Placebo	8.9	(-14.6, 31.8)
Placebo	0/28	(0.0, 12.3)			

N=The total number of patients in the treatment arm.
[1] The 95% CI for the proportion of responders is computed using Clopper-Pearson exact method.
[2] The 95% CI for the difference in proportions is computed using Santner-Snell method.
Source: Table 14.2-2.1

Other secondary efficacy analyses

Changes in PROS lesions

Change from baseline (as assessed by BIRC) in the sum of target lesion volumes

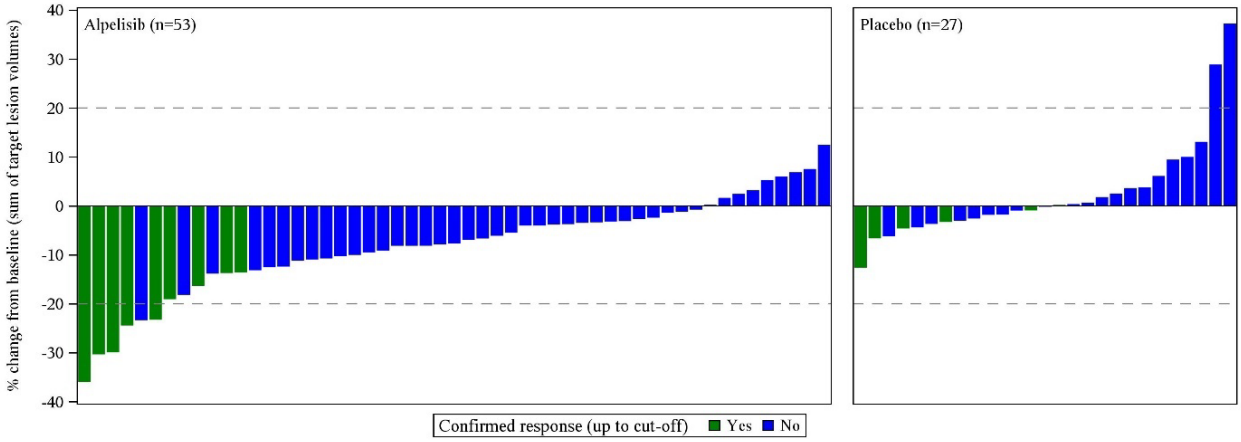
In group 1 the mean (SD) percentage change from baseline in the sum of target lesion volume was -4.6% (12.27) at Week 24 and -8.0% (14.92) at Week 48. The proportion of patients at Week 16 with a decrease in the sum of target lesion volume from baseline was 83.0% in the alpelisib arm and 51.9% in the placebo arm.

In group 2 the mean (SD) percentage change from baseline in sum of target lesion volume was -3.5% (15.17) at Week 24 and -7.7% (17.50) at Week 48. The proportion of patients at Week 16 with a decrease in the sum of target lesion volume from baseline was 69.8% in the alpelisib arm and 31.8% in the placebo arm.

None of the patients achieved response while receiving treatment with placebo.

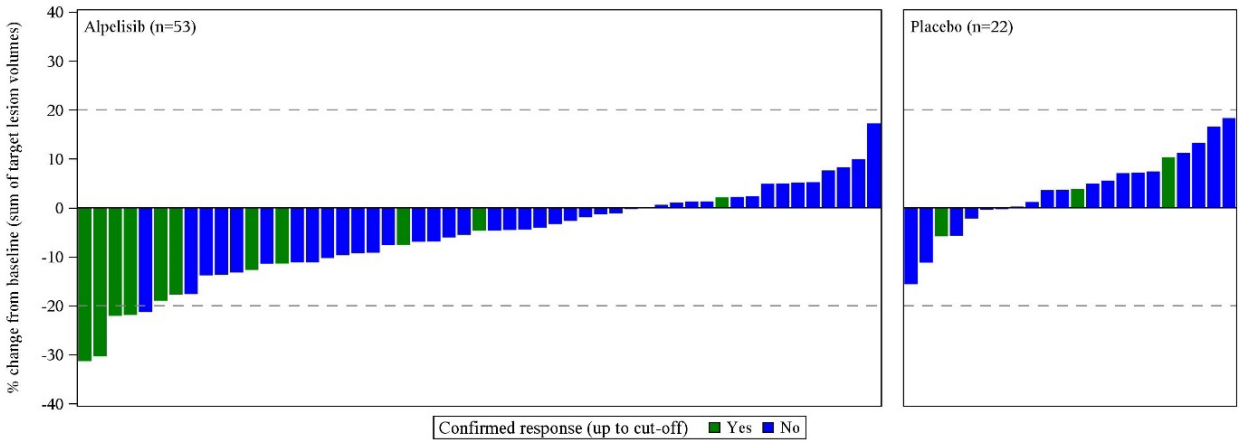
Figure 38 Waterfall plot for percentage change from baseline in the sum of target lesion volumes based on BIRC at Week 16 (FAS)

***Group 1**: Age group ≥ 18yrs, N=81*



Decrease in % change from baseline	83.0%	51.9%
Increase/zero change in % change from baseline	17.0%	48.1%

***Group 2**: Age group 6 - 17yrs, N=84*



Decrease in % change from baseline	69.8%	31.8%
Increase/zero change in % change from baseline	30.2%	68.2%

Patients for whom the % change in sum of target lesion volumes was not available were excluded from the analysis.
Percentages above use n as denominator.
The green bars represent patients who had a confirmed response with alpelisib at any time point up to the cut-off date, including those patients originally randomized to placebo and subsequently transitioned to alpelisib on which they achieved a confirmed response.

Source: Figure 14.2-2.1Source: BYL719 PROS SCE-Figure 3-7

Duration of response

Table 40 Summary of duration of response for patients with confirmed response (FAS - BYL719) cut-off date of 20-Mar-2024

	Group 1 (≥ 18 yrs) Alpelisib N=54	Group 2 (6 – 17 yrs) Alpelisib N=56
n/M (%)	0/9 (0.0)	2/13 (15.4)
Maximum follow-up (weeks)	83.1	80.1
Median follow-up (weeks)	49.1	55.1
Median time to censoring (weeks)	49.1	70.3
% Distribution of duration of response (95% CI)		
24 weeks	100 (100, 100)	100 (100, 100)
40 weeks	100 (100, 100)	90.9 (50.8, 98.7)
48 weeks	100 (100, 100)	90.9 (50.8, 98.7)
72 weeks	100 (100, 100)	79.5 (39.3, 94.5)

Number (M) represents total number of patients included in the analysis (confirmed responders).
Number (n) represents total number of events included in the analysis.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer, Crowley (1982). Distribution of duration of response estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for 95% CIs of KM estimates. For DOR, the start date is the date of first documented response, and the end date is defined as the date of disease progression or death or rescue surgery on any PROS lesion.
Source: Table 14.2-3.13

Supportive efficacy analysis from Group 2

Overall clinical response

Overall clinical response was assessed through a combination of clinical evaluation of the patient's general condition and radiological imaging as assessed by the Investigator. It is reported as improved, stable, worsened or not evaluable.

Table 41 Proportion of patients with overall clinical response by time point and treatment in Groups 1 and 2 (FAS)

		Group 1 (≥ 18 yrs)			Group 2 (6 – 17 yrs)		
Time point	Overall clinical response	Alpelisib arm N=54 n (%)	Placebo arm N=27 n (%)	All adults N=81 n (%)	Alpelisib arm N=56 n (%)	Placebo arm N=28 n (%)	All pediatrics N=84 n (%)
Week 16	Improved	9 (16.7)	2 (7.4)	-	6 (10.7)	4 (14.3)	-
	Stable	43 (79.6)	22 (81.5)	-	48 (85.7)	20 (71.4)	-
	Worsened	0	1 (3.7)	-	2 (3.6)	0	-
Week 24	Improved	13 (24.1)	9 (33.3)	22 (27.2)	13 (23.2)	8 (28.6)	21 (25.0)
	Stable	38 (70.4)	16 (59.3)	54 (66.7)	42 (75.0)	18 (64.3)	60 (71.4)
Week 40	Improved	16 (29.6)	13 (48.1)	29 (35.8)	20 (35.7)	10 (35.7)	30 (35.7)
	Stable	30 (55.6)	10 (37.0)	40 (49.4)	34 (60.7)	16 (57.1)	50 (59.5)
	Worsened	1 (1.9)	0	1 (1.2)	0	0	0
Week 48	Improved	19 (35.2)	13 (48.1)	32 (39.5)	24 (42.9)	11 (39.3)	35 (41.7)
	Stable	25 (46.3)	10 (37.0)	35 (43.2)	29 (51.8)	15 (53.6)	44 (52.4)
	Worsened	1 (1.9)	0	1 (1.2)	1 (1.8)	0	1 (1.2)

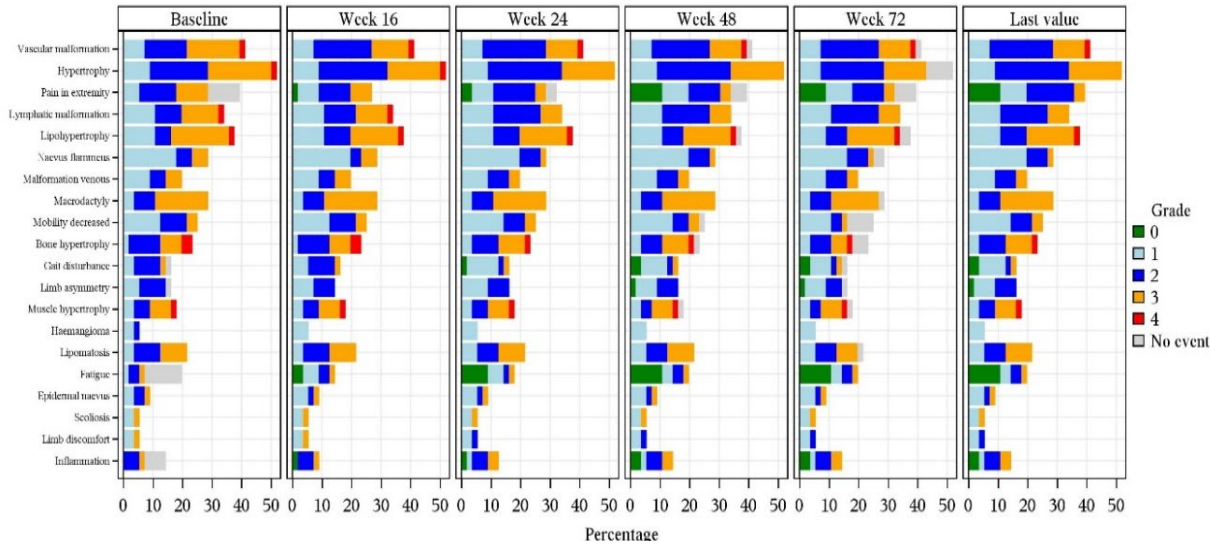
Source: Table 14.2-3.12

Changes in PROS-related signs and symptoms

The evolution of the PROS-related signs and symptoms, severity (from grade 1-4) is displayed at key time-points (i.e. baseline, Weeks 16, Weeks 24, and Weeks 48) (Figure 39).

Figure 39: Shift in CTCAE grade from baseline for the most frequent PROS related medical conditions ongoing at baseline in Group 2 – EPIK-P2 (FAS)

Group 2: age 6 - 17 years, Treatment: Alpelisib arm



The top 20 adverse events are based on the frequency reported in paediatric patients. An event is defined as resolved (denoted Grade 0) if it has an end date with no subsequent event prior to the end of the respective time interval.

Missing means a missing CTCAE grade for an event.
No event at baseline means there was no event present at baseline, but an event subsequently occurred on the study.
No event at other time points means that a patient did not reach that time point on the study.
Week 16 corresponds to last value during placebo-controlled period.
Source: BYL719 PROS SCE-Figure 3-9

Patient Global Impression of Symptom Severity (PGI-S)

At baseline, the majority of patients (55.6%, 40/72) reported no symptoms. Therefore, the results presented here focus on the patients with symptoms at baseline. Out of the 18 patients in the alpelisib arm who reported symptoms (mild to moderate) at baseline, 11 patients (61.1%) improved by at least one category on the PGI-S scale at the last available value, and 2 patients (11.1%) worsened by at least one category.

Pain

Pain was assessed via several questionnaires in paediatric patients in EPIK-P2. No major impact on the improvement of pain was observed. Of note, only a small number of patients were receiving pain medications, and no patients had a history of opioid use prior to the start of treatment with alpelisib. This indicates that pain was not a significant symptom for these patients.

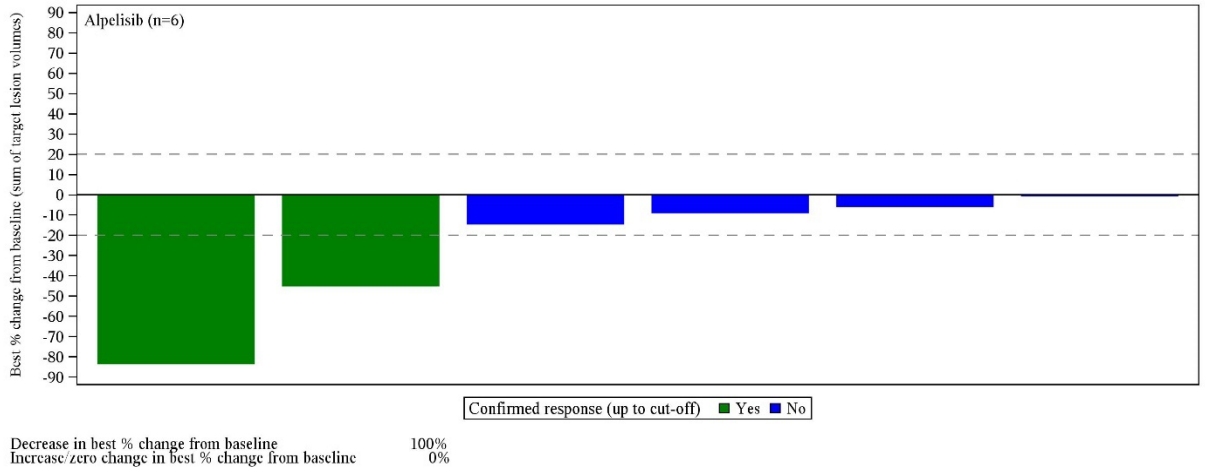
Exploratory efficacy results from Group 4

The proportion of patients with radiological response by BIRC was 28.6% (2/7 patients) at Week 24, and 14.3% (1/7 patients) at Week 48. Of note: 1 patient who was a responder at Weeks 24 had unknown radiological status at Week 48.

All 6 patients with an assessment at Week 24 achieved a reduction from baseline (Figure 41).

Figure 40: Waterfall plot for best percentage change from baseline in the sum of target lesion volumes based on BIRC up to the cut-off date (FAS)

Group 4: Age group 2 - 5 years, N=7



Decrease in best % change from baseline 100%
Increase/zero change in best % change from baseline 0%

Patients for whom the best % change in sum of target lesion volumes was not available were excluded from the analysis.
Percentages above use n as denominator.
The green bars represent patients who had a confirmed response with alpelisib at any time point up to the data cut-off date.
Source: BYL719 PROS SCE-Figure 3-12

Changes in PROS lesions

Change from baseline (as assessed by BIRC) in the sum of target lesion volumes

All 6 patients with an assessment at Week 24 achieved a reduction from baseline. The mean (SD) percentage change from baseline in the sum of target lesion volume was -16.5% (33.13) at Week 48. Overall, 100% of patients achieved a reduction from baseline (**Figure 41** above).

No patient in exploratory Group 4 developed new lesions up to the data cut-off date for primary analysis.

Overall clinical response

At Week 24, all patients in exploratory Group 4 had either improved (3/7; 42.9%) or achieved stable (4/7; 57.1%) overall clinical response. At Week 48, most patients with an evaluable Week 48 assessment had either improved (3/7; 42.9%) or achieved stable (2/7; 28.6%) overall clinical response. Two patients had missing clinical response status at Week 48.

Changes in symptoms and complications/comorbidities associated with PROS

The majority of the patients in exploratory Group 4 had stable PROS-related symptoms/ complications by the last assessment compared to baseline. No significant shift in CTCAE grades for majority of the PROS-related medical conditions occurred.

Exploratory efficacy results from Group 5 (6 to 17 years old starting dose 125 mg)

Proportion of patients with confirmed response over time

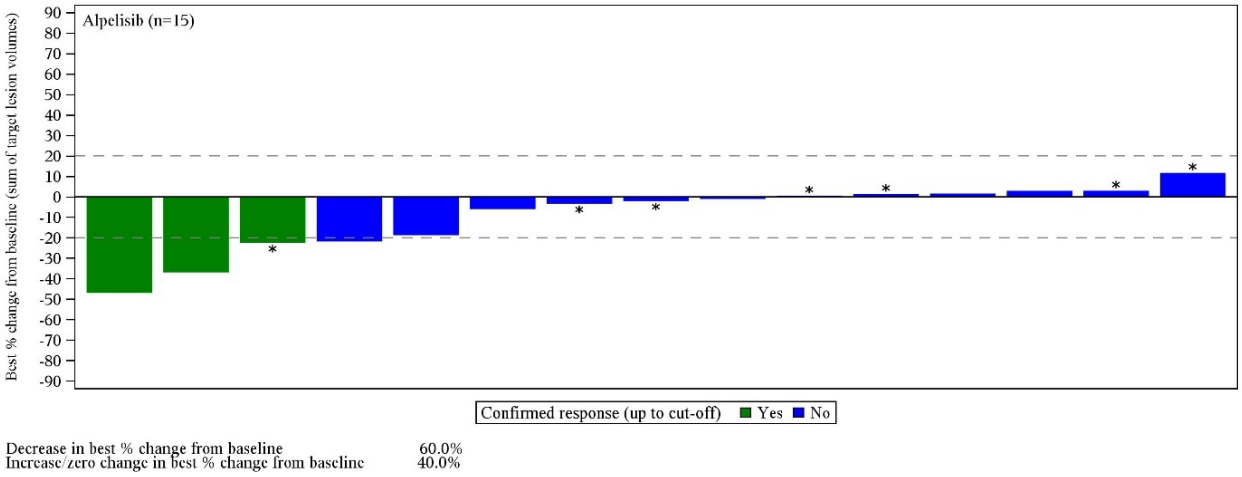
The proportion of patients with confirmed response was 18.8% (3/16 patients).

Proportion of patients with radiological response over time

Among the 12 patients with an assessment at Week 24, 58.3% achieved a reduction from baseline.

The mean (SD) percentage change from baseline in the sum of target lesion volume was -7.9% (16.41) at Week 24. The Figure below shows the best percentage change from baseline in the sum of target lesion volume achieved up to the cut-off date by treatment arm. Overall, 60.0% of patients achieved a reduction from baseline.

*Figure 41 Waterfall plot for best percentage cha*nge from baseline in the sum of *target lesion volumes based on BIRC up to the cut-off date (FAS)*



Patients for whom the best % change in sum of target lesion volumes was not available were excluded from the analysis.
Percentages above use n as denominator.
** Best % change achieved at Week 16.*
The green bars represent patients who had a confirmed response with alpelisib at any time point up to the cut-off date.
Source: Figure 14.2-1.2

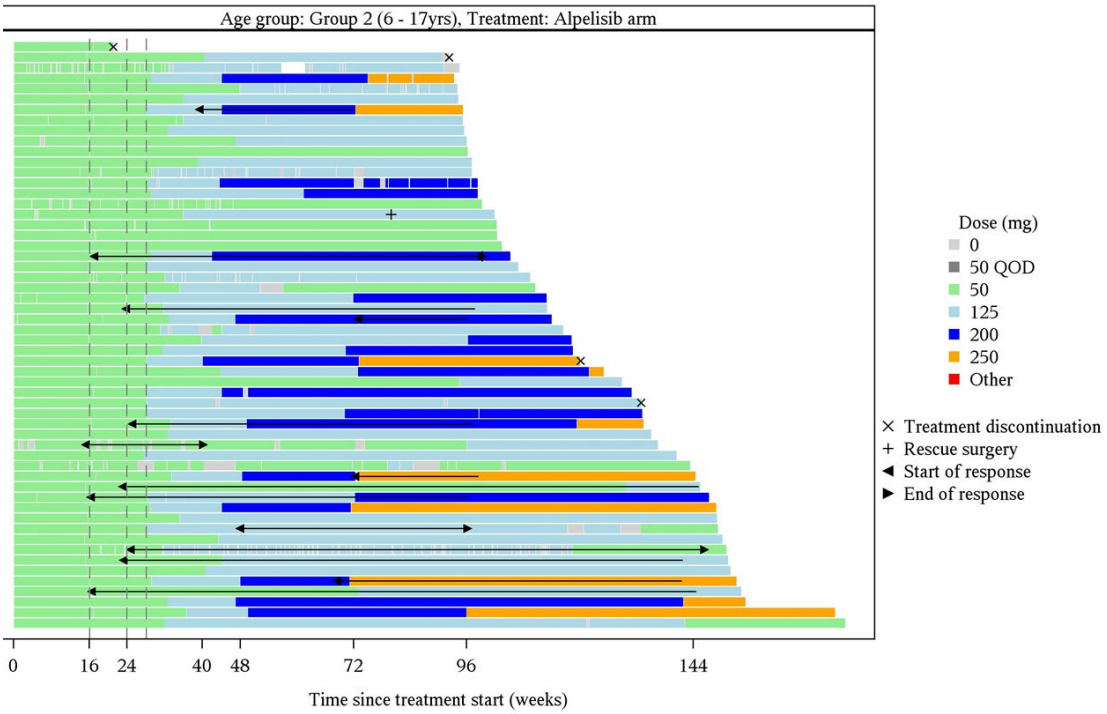
Summary of Group 2 and exploratory Group 4 efficacy data with approximately 6 months additional follow-up (data cut-off date: 25-Sep-2024)

Group 2 interim analysis

With approximately 6 months additional follow-up (data cut-off date: 25-Sep-2024), the proportion of patients with confirmed response was assessed. No formal analysis was planned to be performed. Additional data since the primary analysis that became available are presented below:

Proportion of patients with confirmed response (additional follow-up since the primary analysis): The proportion of patients in Group 2 randomized to alpelisib with a confirmed objective response is 25.0% (14/56 patients) with 97.5% CI: 13.2, 40.3. Compared to the primary analysis, there is 1 additional confirmed responder with late confirmation of response (Week 96) following dose escalation. Three patients (2 in the alpelisib arm and 1 in the placebo arm) required rescue surgery while on alpelisib treatment (Figure below).

Figure 42 Dose of study treatment over time and confirmed response by BIRC (FAS)



Dashed vertical lines correspond to the planned study days for Week 17 Day 1, Week 24 Day 1 and Week 29 Day 1
Other: Non protocol specified dose regimen for example: Overdose (100 mg, 150 mg, 400 mg) and wrong regimen (125 mg QOD)
Source: BYL719 PROS SCE-Figure 3-13

Duration of response: In the additional analysis with the cut-off date of 25-Sep-2024, the median duration of response was estimated to be 121.6 weeks (95% CI: 48.3, NE) with a median follow up of 73.6 weeks at the data cut-off date. Three out of 14 patients had progressive disease, and 1 patient needed rescue surgery, but all 4 patients remained on treatment. Twelve out of the 14 patients with confirmed response were still responding by BIRC at the last MRI assessment prior to the data cut-off date.

Exploratory Group 4 interim analysis

Proportion of patients with confirmed response: The proportion of patients who achieved confirmed responder status remained unchanged from the primary analysis (2/7 patients (28.6%; 97.5% CI: 2.5, 75.2)).

Exploratory Group 5 interim analysis

The proportion of patients with confirmed objective response is 25.0% (4/16 patients) with 95% CI: 7.3 to 52.4 with one more responder

During the procedure, the Applicant provided data from week 96 interim analysis (cut-off 18-Feb-2025) corresponding to ~10 additional months of follow-up compared to the primary analysis and ~2.5 years of median exposure to alpelisib.

Proportion of patients with confirmed response

In Group 2, 3 new confirmed responders were observed in the alpelisib arm, compared to the primary analysis (16/56 participants, 28.6%, 97.5% CI: 16%-44.1%) and 2 additional confirmed responders were observed in patients who switched to alpelisib after the placebo-controlled period.

Tree more confirmed responders were observed in Group 1 alpelisib arm, and two in Group 5; 1 additional confirmed respondese was observed in patient who switched to alpelisib after the placebo-controlled period in Group 1.

Table 42 Proportion of participants with confirmed objective response by BIRC – Alpelisib period

	Group 1 (>=18yrs)		Group 2 (6 - 17yrs)		Group 4 (2 - 5yrs)	Group 5 (6 - 17yrs)
	Alpelisib N=54	Switched to Alpelisib after W16 N=26	Alpelisib N=56	Switched to Alpelisib after W16 N=26	Alpelisib N=7	Alpelisib N=16
Responder: n (%)	11 (20.4)	7 (26.9)	16 (28.6)	7 (26.9)	2 (28.6)	5 (31.3)
Clopper-Pearson (Exact) 97.5% CI	(9.6, 35.4)	(10.1, 50.6)	(16.0, 44.1)	(10.1, 50.6)	(2.5, 75.2)	(9.3, 62.0)
Clopper-Pearson (Exact) 95% CI	(10.6, 33.5)	(11.6, 47.8)	(17.3, 42.2)	(11.6, 47.8)	(3.7, 71.0)	(11.0, 58.7)

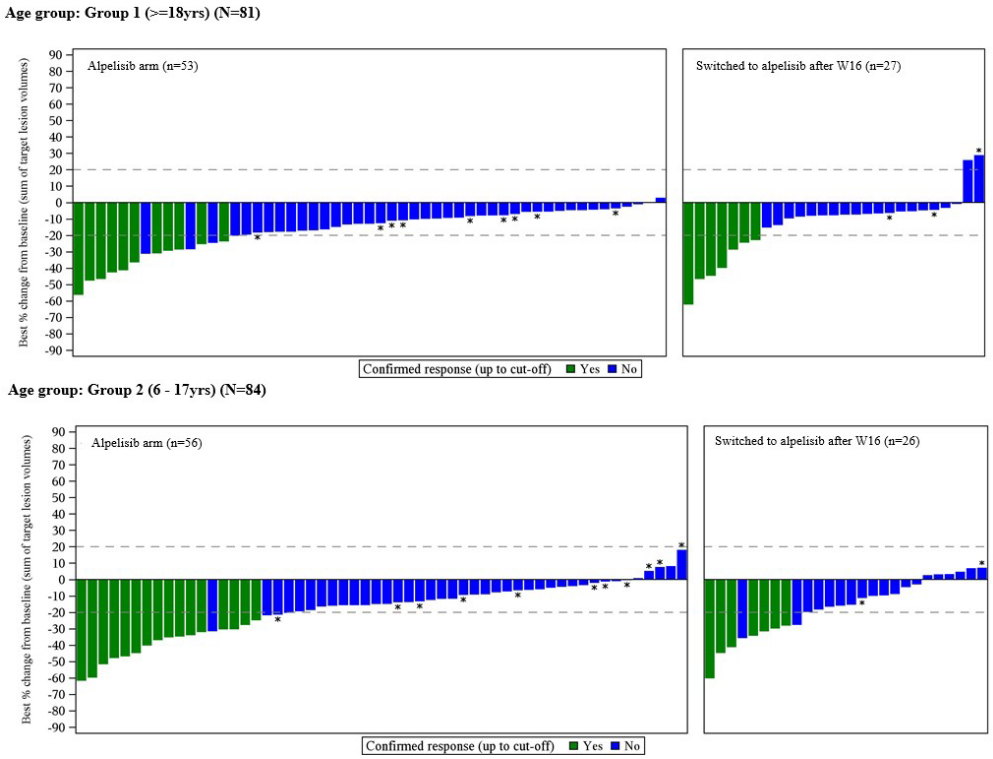
Source: [EPIK-P2 Week 96 analysis CSR-Table 11.1]

All new confirmed responses observed in patients randomized to alpelisib in Groups 1 and 2, were achieved after dose escalation to 200 mg (except from one adult patient who remained in the starting dose).

Change from baseline (as assessed by BIRC) in the sum of target lesion volumes

Figure 45 below illustrates the best percentage change from baseline in Groups 1 and 2 in the sum of target lesion volumes up to the last available imaging assessment prior to the cut-off date for the Week 96 analysis.

Figure 43 Waterfall plot for best percentage change from baseline in the sum of target lesion volumes based on BIRC up to the cut-off date (FAS)



Participants for whom the best % change in sum of target lesion volumes was not available were excluded from the analysis.
* Best % change achieved at Week 16 (i.e., end of placebo-controlled period).
Source: [EPIK-P2 Week 96 Analysis CSR-Figure 14.2-1.2]

Duration of response

In Group 2, the median duration of response for the 16 confirmed responders randomized to alpelisib arm was estimated to be 121.6 weeks (95% CI: 82.3, NE) with a median follow up of 78.2 weeks.

Four out of 16 patients had progressive disease, and 1 patient needed rescue surgery, but all remained on treatment. The remaining 11 patients with confirmed response were ongoing treatment and continuing to respond by BIRC at the last MRI assessment prior to the data cut-off date.

Overall clinical response

In Group 2, at the Week 96 analysis, as 46.4% of patients in Group 2 had improved overall clinical response was based on patient's general condition and radiological imaging as assessed by the Investigator.

5.3.3. Clinical studies in special populations

No patients over 65 years were enrolled in any of the below mentioned studies.

No specific studies were conducted in patients with renal or hepatic impairment for this application.

Table 43 Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	NA	NA
Hepatic impairment** patients (Subjects number /total number)	NA	A2105: 12/23 (6 subjects with moderate and 6 with severe hepatic impairment)
Paediatric patients <18 years (Subjects number /total number)	EPIK-P3 (upfront placebo controlled): 107/188[1] [1] enrolment still ongoing	EPIK-P1: 39/57 EPIK-P3, retrospective part: 34/48 EPIK-P3, prospective part: 31/40

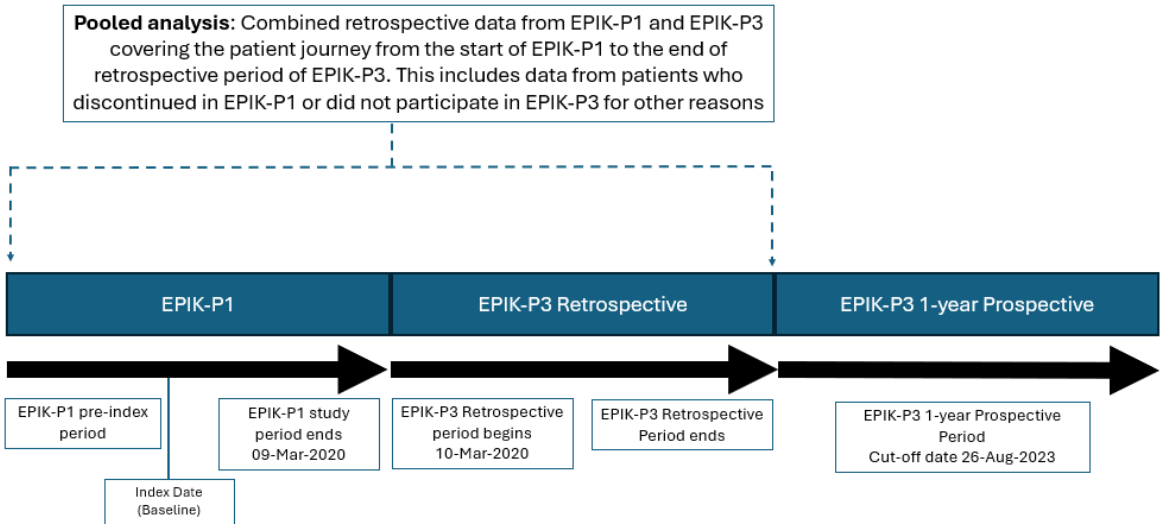
** Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)*
*** Hepatic impairment is defined as having Child-Pugh score B or C*
Source: BYL719 PROS Clinical Overview-Section 1.2.1

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

Efficacy data were not pooled given the differences in efficacy assessments (i.e. qualitative vs. quantitative assessments as well as different timepoints for the assessments).

EPIK-P1 and the retrospective period from EPIK-P3 contain retrospectively collected data from the same patients allowing for an assessment of the patient journey from the start of EPIK-P1 until the end of the retrospective period of EPIK-P3 (under the compassionate use program). The patients' journey is depicted Figure 46.

Figure 44: Patient journey EPIK-P1 to EPIK-P3



Source: BYL719 PROS SCS-Figure 1-1

Patient population

A total of 58 patients were included in EPIK-P1. Fifty-seven were included in the full study. As of the EPIK-P1 data cut-off date, 91.2% (52/57) of patients were receiving treatment with alpelisib, and 48 of these patients consented to participate in the retrospective period of EPIK-P3.

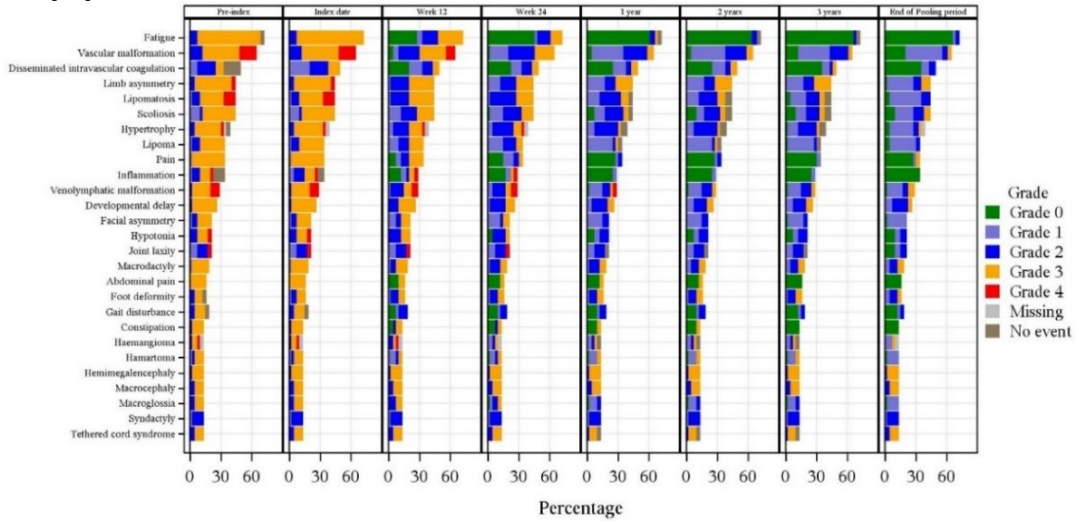
Efficacy results

PROS-related signs and symptoms

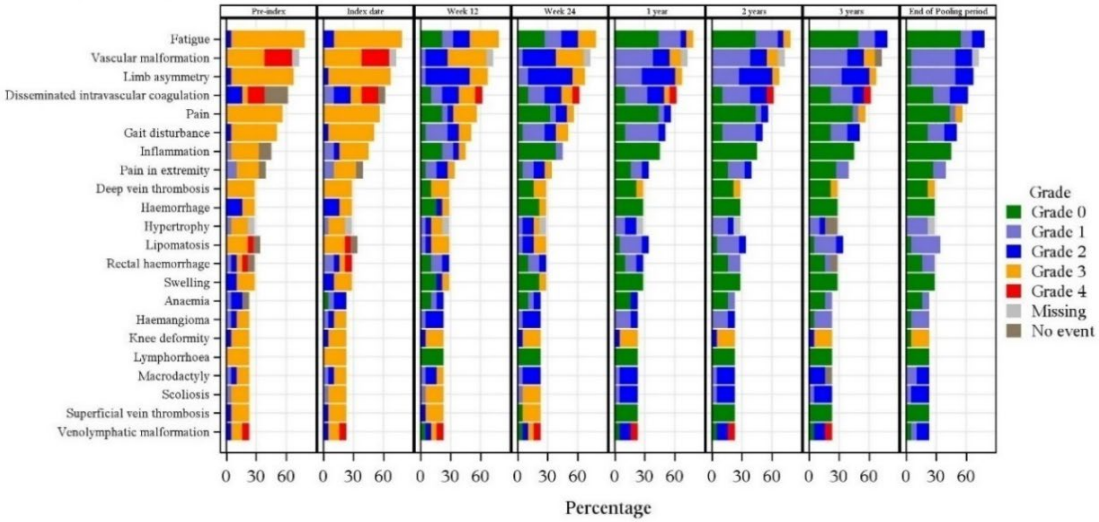
The pooled data from EPIK-P1 and the retrospective period of EPIK-P3 showed that there was a decrease in PROS-related signs and symptoms over time (as measured by Common Terminology Criteria [CTC] grade).

Figure 45: Shift in CTCAE grade from index date for the most frequent PROS-related signs and symptoms by age category-EPIK-P1+P3 retrospective period (Full study population)

Paediatric population:



Adult population:



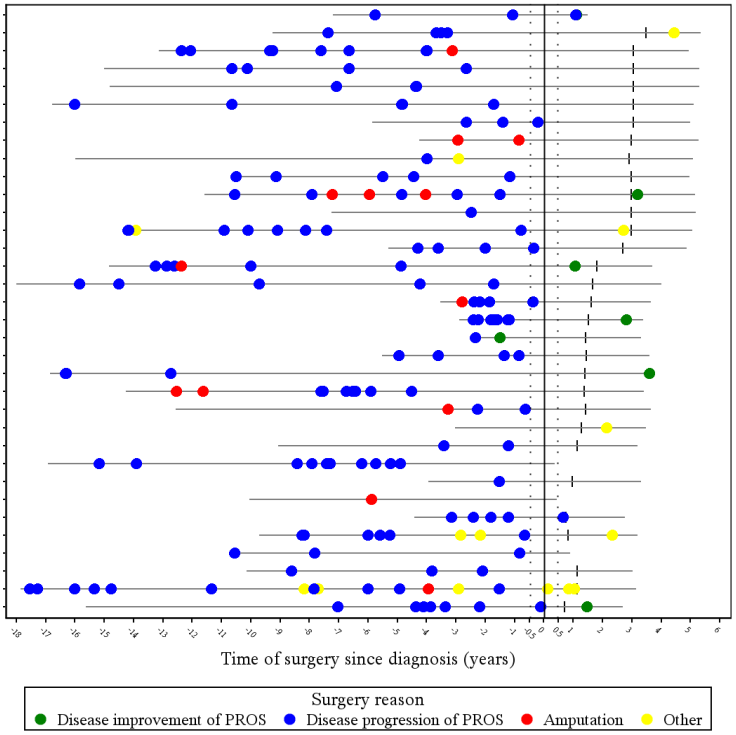
The top 20 PROS-related signs and symptoms are based on the frequency reported in pediatric and adult patients at the start of the index date (Day 1).
An event is defined as resolved (denoted Grade 0) if there is an end date with no subsequent event prior to the end of the respective time interval.

Source: BYL719 PROS SCE-Figure 3-2

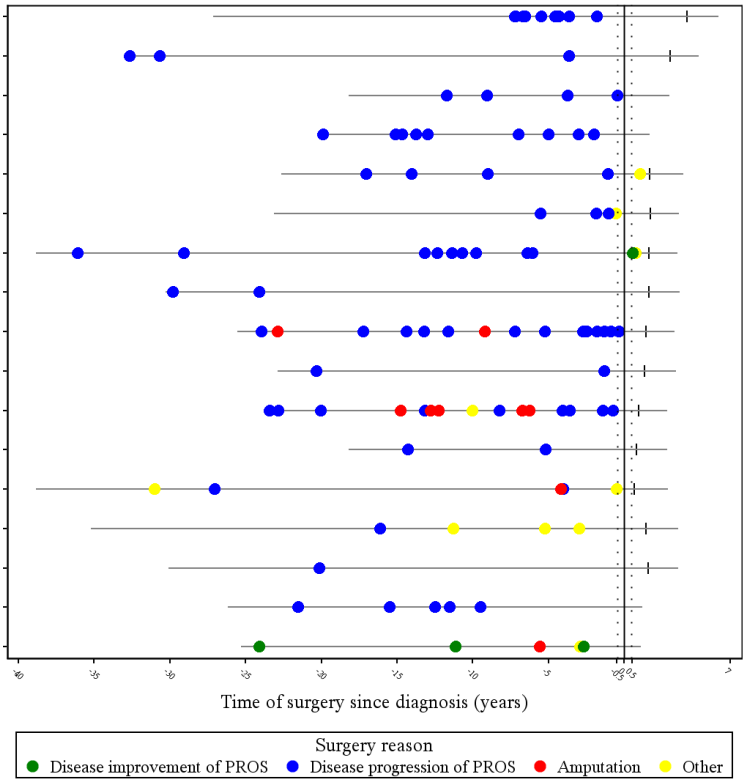
Surgeries for the management of PROS

Figure 46: PROS-related completed surgeries from diagnosis to end of the pooling period by age category – EPIK-P1+P3 retrospective period (Full study population)

Peadiatric Patients



Adult patients



The dots represent the occurrence of surgery. The red dots indicate a surgery for an amputation. Completed surgeries are reported. X axis is from patient diagnosis until the end of pooling period. Dotted lines refer to -24 weeks and +24 weeks from index date. Vertical bars indicate start of the EPIK-P3 retrospective period at the patient level.
Surgeries Categorized as 'Other' following initiation with alpelisib are explained in EPIK-P1+P3 retrospective period pooled report-Section 10.2.3, Figure 14.3-1.
Source: BYL719 PROS SCE-Figure 3-3

Other efficacy endpoints (EPIK-P1 and EPIK-P3)

Hospitalization for the management of PROS

In paediatric patients, the mean number of hospitalizations related to PROS was 1.7 (SD: 1.59). Eleven (28.2%) patients had 1 hospitalization, 2 (5.1%) patients had 2 hospitalizations, and 2 (5.1%) patients had more than 2 hospitalizations related to PROS. One patient had a missing start and end date so 14 patients were used to calculate the median duration of 12.5 days (range: 2-310).

In adult patients, the mean number of hospitalizations related to PROS was 1.0 (SD: 0.00). Four (22.2%) adult patients had 1 hospitalization related to PROS, with a median duration of 8.5 days (range: 4-31).

Karnofsky/Lansky performance status

Among paediatric patients, the median Lansky score at the index date was 70.0 (range: 20 to 100) and the median Karnofsky score at baseline was 70.0 (range: 40-90. At the last available post-index assessment, the majority of paediatric patients (78.8%) had an improved score.

Among patients who were of adult age at the end of the pooling period, the median Karnofsky score at the index date was 60.0 (range: 20 to 100). At the last available post-index assessment, the majority of adult patients (85.7%) had an improved score.

5.3.5. Observational data

Managed Access Program (MAP)

During the procedure, the Applicant provided data from Managed Access Program (MAP) that covers the period from from 11-Jan-2016 (the date of first treatment under the ATU in France) to 31-AUG-2025 (the cut-off date for this analysis). A total of 945 patients with diagnosis of severe or life-threatening PROS and preferably evidence of a mutation in the PIK3CA gene were approved to receive alpelisib therapy in a total of 36 countries: France (n=319; 33.8%), United States (n=199; 21.1%), and Spain (n=86; 9.1%). The median age of patients was 13 years (range: 0-79); 618 were pediatric patients (median age: 8 years, range 0-17 years; 3.6% were 0-1 years of age, 19.8% were 2-5 years of age, 23.9% were 6-11 years of age, and 18.1% were 12-17 years of age) and 327 were adult patients (median age: 31 years, range 18-79 years). In majority of patients (59.2%), PROS Disorder type was not specified.

Table 44 PROS phenotypes of age category (Full Analysis Set)

Disorder type	0-1 years N=34 n (%)	2-5 years N=187 n (%)	6-11 years N=226 n (%)	12-17 years N=171 n (%)	Pediatric patients N=618 n (%)	Adult patients N=327 n (%)	All patients N=945
PROS Disorder type not specified in GEMS	14 (41.2)	109 (58.3)	125 (55.3)	97 (56.7)	345 (55.8)	214 (65.4)	559 (59.2)
CLOVES syndrome	9 (26.5)	42 (22.5)	41 (18.1)	39 (22.8)	131 (21.2)	77 (23.5)	208 (22.0)
KTS (Klippel-Trenaunay Syndrome)	1 (2.9)	7 (3.7)	23 (10.2)	12 (7.0)	43 (7.0)	17 (5.2)	60 (6.3)
MCAP or M-CM (Megalencephaly-Capillary Malformation)	6 (17.6)	8 (4.3)	16 (7.1)	11 (6.4)	41 (6.6)	2 (0.6)	43 (4.6)
Isolated Lymphatic Malformation	2 (5.9)	3 (1.6)	5 (2.2)	4 (2.3)	14 (2.3)	5 (1.5)	19 (2.0)
FIL (Facial Infiltrating Lipomatosis)	1 (2.9)	6 (3.2)	7 (3.1)	3 (1.8)	17 (2.8)	0	17 (1.8)
Macrodactyly	1 (2.9)	6 (3.2)	3 (1.3)	2 (1.2)	12 (1.9)	3 (0.9)	15 (1.6)
FAVA (FibroAdipose Vascular Anomaly)	0	1 (0.5)	1 (0.4)	3 (1.8)	5 (0.8)	3 (0.9)	8 (0.8)
HME (HemiMegalEncephaly)	0	1 (0.5)	1 (0.4)	0	2 (0.3)	3 (0.9)	5 (0.5)
CLAPO syndrome	0	1 (0.5)	2 (0.9)	0	3 (0.5)	1 (0.3)	4 (0.4)
FAO (FibroAdipose hyperplasia or Overgrowth)	0	2 (1.1)	2 (0.9)	0	4 (0.6)	0	4 (0.4)
Muscular HH (HemiHyperplasia)	0	1 (0.5)	0	0	1 (0.2)	1 (0.3)	2 (0.2)
HHML (HemiHyperplasia-Multiple Lipomatosis)	0	0	0	0	0	1 (0.3)	1 (0.1)

The median dose for pediatric patients was 50 mg (range: 20-250 mg) and 250 mg (range: 50-300 mg) for adult patients.

No formal efficacy evaluation was performed. However, using the re-supply requests as a surrogate measure, the estimated overall median duration of treatment was 17.7 months; 17.9 months for pediatric patients (14.1 months for patients 0-1 years of age, 19.9 months for patients 2-5 years of age, 18.3 months for patients 6-11 years of age, and 16.9 months for patients 12-17 years of age) and 16.9 months for adult patients.

The longest estimated exposure duration was 84 months in pediatric patients and 85 months in adult patients and 53% of patients had their status recorded as "Treatment ongoing" at the time of the data cut-off.

Natural course of the disease from patient survey

The platform includes from patients in the US, UK and Canada with genetic diagnosis of PROS who consented for their medical history to be captured. Focused data on patients or time periods without exposure to alpelisib were collected from 40 PROS patients (30 from the US, 8 from Canada and 2 from the UK). Of the 40 patients, 31 were pediatrics (median age: 2 years, range 0-17 years) and 9 were adults (median age: 37 years, range 25-52 years), at diagnosis. The majority (20 of 40; 50.0%) of the patients had a PROS subtype of CLOVES and the subtype aws unknown for 8 patiets (25.8%)

All patients underwent at least one surgery, and 30 patients (75.0%) had more than two surgical procedures. The median number of surgeries per patient was 6 (range: 1 to 22).

5.3.6. Early dialogue with CHMP

In the framework of early dialogue with patients, the CHMP has received the following input from EURORDIS:

PROS as unmet medical needs. impact on quality of life

PROS – PIK3CA related overgrowth spectrum includes 14 phenotypes, and the impact on daily life varies by subtype, or by severity (some forms are relatively benign, others are severe, a full spectrum exists, and this can influence the decision to take a medicine such as alpelisib, if authorised).

Severity is difficult to define, and the opinion of the patient himself/herself should prevail. Facial infiltration with no functional consequences can still provoke severe social isolation and/or deteriorated self-image. Life-threatening manifestations should not be the only element to consider when assessing severity. Inability to walk relatively long distances could also define a severe form.

People with fibroadipose infiltrating lipomatosis or facial infiltrative lipomatosis suffer from infiltration of the cheeks, the tong, the teeth, the ears, with facial distortion and subsequent social isolation. Dentition often needs to be replaced. Oedema can be massive and severe, with 20 to 30kg of weight gain.

A survey among Dutch parents and patients, both children and adults, revealed the proportion of patients who reported being severely affected by difficulties due to staring, questions, or comments.

Painful inflammation and lymphangitis or vascular malformations / venous malformations can be associated with intense itching, night and day, and major difficulties to walk long distances (one person reported not being able to walk for more than 15 minutes) or to use arms. In Dysplastic megalencephaly (DMEG), hemi-megalencephaly (HMEG) and focal cortical dysplasia (FCD), neurological complications can prevail, with seizures, and developmental / cognitive delays, not necessarily life-threatening (although some seizures might be).

Another survey among 145 patients in the Netherlands showed that 107/145 experience pain, with a median numerating rating scale of 6/10. Pain can also define severity for these conditions.

Different functions can be affected, for example a lesion of the tong might completely prevent eating, and surgery can be needed every two years, and this should also define a severe form.

When legs are affected, in moderate to severe cases the patient needs to use a wheelchair.

Evolution of the lesions after surgery or other treatments

The long-term efficacy of surgical and interventional treatments is often limited. Lesions frequently recur within weeks of excision, with some patients undergoing multiple surgeries over decades without durable benefit. Limb surgery yields only transient improvement; joint destruction may ultimately necessitate orthotic support, and spinal bracing can markedly impair quality of life. Liposuction may temporarily reduce adipose-related lymphangitis or oedema, with longer-lasting benefit in mild to moderate cases, but carries procedural risks, including significant haemorrhage. Oedema management via lymphatic drainage provides only short-lived relief. Pharmacological options such as sirolimus can modestly reduce pain, pruritus, and swelling, but show poor efficacy in severe forms, with approximately 20% of patients non-responsive. Laser therapy can effectively treat superficial vascular malformations, while sclerotherapy offers limited symptomatic improvement and requires repeated sessions. Hormonal fluctuations during puberty, pregnancy, and menstruation commonly exacerbate pain and lesion progression.

Effects of painkillers, surgery and other treatments on pain

The survey among 145 patients in the Netherlands showed the self-assessed effects of several treatments on pain.

Spontaneous resolutions

None of the patients reported spontaneous resolution of lesions of different nature. In the best case the lesion stabilises. Only one reported spontaneous improvement of nose bleeding due to vascular / veinous malformation, with episodes that culminated at 5 per week for two years, and then to one per month with no intervention. In megencephaly and other forms with overgrowth of the brain, including hemi-megencephaly, it seems the brain growth is more important during the first two years of life, and then the growth stabilises.

Expected benefits in new medicines, in relation to possible side effects

A women explained she would abstain from asking alpelisib immediately, even if the burden of the organisation of care for her kid was evaluated as high, with intensive monitoring. This is due to the unknown benefits and possible risks if alpelisib is used during a child growth, and lack of information on effect on fertility.

Among patients with the CLOVES form, where the risk of malignancy is higher, alpelisib could overweigh risks more often, but again malignancy and/or life-threatening lesion should not be the only criteria to define severity for the indication of alpelisib.

Patients and parents are of the opinion that it should not be delayed too long after diagnosis, as the earlier it is started, the smaller the lesions.

Cognitive impairment (or learning difficulties), another severity criteria, can affect children and parents might be more inclined to expose their children to side effects if the medicine could prevent cognitive loss or even restore some functions.

Other aspects of the disease and its progression useful for the assessment

Some patients reported that symptoms seem to be exacerbated by physical activity and suggested to take alpelisib on demand when activity increases, rather than every day.

Alternative administration modes (continuous uptake life-long raised safety concerns) should be considered: every second day dosing, intake only during periods for women, structured treatment interruptions etc.

Patients are also questioning if alpelisib could be delayed until next surgery would be planned, and initiated shortly before, to prevent regrowth after a lesion has been removed.

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

The Applicant applied for a conditional MA for Vijoice (alpelisib) for the following indication:

Vijoice is indicated 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.

Since 2016, alpelisib is used within a compassionate use program in France (ATU). Venot et al (2018) described data from 19 patients with PROS treated with alpelisib in a single centre; Following this publication, the applicant issued a global Managed Access Program (MAP; Treatment Plan) in Nov-2018 extending the treatment to additional patients and outside France. The applicant applied for a MA in Jun-2022 for the treatment of patients with PROS. This application was however withdrawn in Oct-2023 as prospective data from Study EPIK-P2 could not be provided to address the CHMP questions within the procedural timeframe. In the current application, new data was added to what was already submitted in the previous application, deriving from the controlled study EPIK-P2 and an update from the EPIK-P3 study.

The current application is based on a pivotal retrospective chart review in patients with PIK3CA Related Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK P1), an ongoing phase II study that aimed to evaluate the long-term safety and efficacy of alpelisib in patients with PROS who previously participated in Study EPIK-P1 (EPIK-P3) and a supportive ongoing Phase II study with an initial 16-week, randomized, double-blind, placebo-controlled period in paediatric and adult patients with PROS (EPIK-P2).

The prospective period of EPIK-P3 and study EPIK-P2 are currently ongoing.

Design and conduct of clinical study

EPIK-P1

This study was a retrospective chart review of patients 2 years of age and older with severe or life-threatening PROS who have received alpelisib at least 24 weeks before the abstraction date as part of a compassionate use program. EPIK-P1 aimed to collect data from medical charts across different sites and described the clinical and functional outcomes in patients treated under compassionate use programs. This retrospective study was based on routine clinical data with no standard visit assessment schedule.

For inclusion in the compassionate use program, patients had to have a confirmed/documented diagnosis of PROS and the patient's condition had to be assessed by the treating physician as severe or life-threatening and a treatment deemed necessary.

No formal dose finding study was conducted. The dosage regimen used was based on the lowest available strength of alpelisib tablets for paediatric patients (i.e. 50 mg) and the lowest dosage used in breast cancer clinical trials that were ongoing at the time for adult patients (i.e. 250 mg).

The primary endpoint was the proportion of patients with response defined as a reduction ≥ 20% in the sum of measurable target lesion volume (1 to 3 lesions), provided that none of the individual target lesions have ≥ 20% increase from the index date and in the absence of progression of non-target lesions and without new lesion at Week 24 in the complete case population (a subset of the efficacy population with 32 patients included).

While no formal definition of response exists for PROS, in order to contextualize the responder definition proposed by the applicant, an analogy could be made with the RECIST 1.1. criteria (e.g., partial response: at least a 30% decrease in the sum of the largest diameters of the target lesions compared to the baseline lesion diameter; Progression: At least a 20% increase in the sum of the largest diameters of the target lesions, taking the smallest sum obtained during follow-up as a reference).

In an attempt to improve the standardisation of data, the primary imaging analysis for the primary endpoint and some secondary endpoints were performed by an independent central radiology review: the target lesions (1 to 3) were independently selected via independent central radiology review using the pre-index date scans and clinical information provided by the treating physicians. Subsequently trained readers read participants scans according to a two (2)-reader, Sequential Time Point, batch read mode paradigm. The secondary outcome measures related to tumour decrease were: changes in the sum of measurable target lesion volume, changes in the sum of all measurable (target and non-target) lesion volumes over time.

The clinical secondary endpoints covered changes in the concomitant PROS-related medications, PROS-related non-drug treatments and other medical interventions, PROS-related surgery, Changes in PROS symptoms and complications, pain, changes in functional status, changes in healthcare resource use (HRU), Physical findings, and Vital signs. The clinical secondary endpoints covered a wide range of clinical outcomes, which were considered critical to demonstrate the clinical relevance of the observed tumour reduction in the heterogeneous manifestations of PROS.

Several major issues related to this study are identified and related to:

• The study design: retrospective chart review; no standard visit assessment schedule; clinical outcomes collection was not standardized; mitigation plans insufficient to compensate for the lack of prospective comparative data.

• No dose-finding studies to support the proposed dosing in adults and paediatric patients.

• Population: PROS population is very heterogeneous by default, due to encompassing several different phenotypes and types of lesions. In addition, the overall small number of patients and the lack of an universally accepted definition for disease severity hampers the extrapolation to a broad indication; responders were from a specific subtype, which questions the extrapolation to other sub-types.

Populations of analyses:

The Full study population (n=57) included all patients who satisfied the study inclusion criteria. This population set was used for all secondary and exploratory efficacy analyses and for safety analyses.

The Efficacy population (n=37) was a subset of the Full study population, which was used for the analysis of the primary endpoint and included patients who met the following criteria:

- Patients with at least one target lesion.

- Patients with an imaging scan performed on the index date.

The complete cases (n=32) was a subset of the Efficacy population, which was used for the analysis of the primary endpoint and included patients who met the following criteria:

- Patients with at least one target lesion.

- Patients with an imaging assessment at both the index date and at Week 24.

EPIK-P3

This study is an ongoing retrospective and prospective open label study that aims to evaluate the long-term safety and efficacy of alpelisib in patients with PROS who previously participated in Study EPIK-P1 and continued to receive treatment with alpelisib after the EPIK-P1 cut-off date.

Fifty patients (88%) were selected in France (44 coming from Necker hospital and 6 from two other French sites), the 7 remaining patients being sparsely distributed in 4 other countries. With this re-submission of the MA application, 1-year data from the prospective period has been provided as new data not provided in the previous submission.

The primary outcomes of this study were focused on safety (e.g., incidence of new/worsening grade ≥ 3 emergent AEs), while efficacy outcomes (e.g., overall clinical and lesion response, PROS-related signs/symptoms/surgeries) were pre-defined as secondary endpoints.

The response to alpelisib was assessed by the investigators who determined whether the condition of the patient had improved, remained stable, or worsened. The response was assessed in terms of the "overall clinical response" (a combination of clinical evaluation of the patient's general conditions and radiological imaging), and the "overall lesion response" (based on radiological imaging and other methods of measurement (e.g., circumference measured by rulers)).

For this study the applicant has described the estimand framework and how patients who discontinue or die before the end of the study will be handled. These patients will be excluded from the denominator for the subsequent yearly intervals. This approach is aligned with the main objective of the study which focuses on assessing long-term safety and tolerability. Therefore, no concerns are raised in this regard. Moreover, populations and sub-group analyses are briefly described. In addition, the sample size for assessing the study objective was not determined based on power calculations or statistical assumptions but given the aim of the study, this is acceptable.

Of the 57 patients who previously participated in EPIK-P1, 52 were eligible for participation in EPIK-P3 (had at least one dose of alpelisib after the EPIK-P1 cut-off date (09-Mar-2020)) and 48 were included in the retrospective part. Among them, 40 patients were subsequently included in the prospective part the study. At last data cut off (15-JUL-2025), 97.5% of patients (39/40) were still on treatment.

It is noted that the limitations regarding dose-selection, population and efficacy outcomes that were highlighted with EPIK-P1 are also present in EPIK-P3 (prospective period) as well.

Pooled analyses of studies EPIK-P1 and EPIK-P3 (retrospective period) have been provided, focusing solely on the characterisation of the alpelisib effect on PROS-related signs/symptoms and surgeries. However,

the retrospective nature of the data is a major limitation to interpret these results. Therefore, data from the pooled analyses are considered merely informative.

EPIK-P2

This is a Phase II multi-centre trial with an initial 16-week, randomized study that included a 16 week, double-blind, placebo-controlled period, followed by two extension periods in paediatric and adult patients with PROS. This is the only prospective, controlled study conducted with alpelisib to assess the efficacy and safety of alpelisib in PROS across both adult and paediatric populations. The comparison with placebo was conducted at an early time point (i.e., 16-weeks) and was set as a secondary outcome. Further, due to some relevant differences (e.g., broader patient population than the target population and different dosage than the intended for marketing), this study is considered supportive.

This multinational study was conducted in patients with PROS irrespective of disease severity. Patients with symptomatic and/or progressive overgrowth and at least one measurable lesion as confirmed by BRIC. The population in this study is broader than the target population (i.e. patients with severe or life-threatening disease), since inclusion was allowed irrespectively of disease severity. Besides, the lack of a universally accepted definition of severe disease is a limitation for the extrapolation of results and has implications on the external validity across the PROS clinical program results.

The following 5 groups were assessed in the study:

Main Groups: 1 (adult patients) and 2 (paediatric patients 6 to 17 years old)

In these groups, patients were randomized in a 2:1 ratio to alpelisib or placebo; after 16 weeks, patients randomized in the placebo arm were switched to active treatment with alpelisib and continued treatment in an open label manner during 2 extension periods.

The starting dose was 125 mg qd with food in adult and 50 mg qd with food in paediatric patients. Dose remained stable during the placebo phase and once the patient had reached at least week 25, increased dose to 200 mg qd and 250 mg qd for adult and 125 mg and 250 mg qd for paediatric patients was possible for response optimization. This recommendation in the paediatric population is mostly empirical and currently lacks evidence, since results from groups 5 are not yet available to support them.

The staring dose tested in adults (i.e., 125 mg qd with food) is half of the dose intended for registration (i.e., 250 mg qd with food) and also half of the one used in EPIK-P1 and EPIK-P3 (250mg QD taken without food), which raises question regarding the value of the result in this group in the context of the evaluation of the MAA and limits data in the adult population to results from EPIK P1.

Exploratory groups: 3, 4 and 5 (paediatric patients)

Those are 3 paediatric, open label exploratory groups that aimed to asses a children friendly granule formulation in patients aged 2 to 5 years old (group 3), exploratory starting dose 50 mg qd in patients aged 2 to 5 years old with possible escalation once patients had reached 6 years old for response optimization (group 4) and a higher starting dose of alpelisib (125 mg) in paediatric patients 6 to 17 years of age (group 5).

Only results from groups 1, 2, 4, and 5, were included in the primary and interim analysis clinical study report.

Endpoints

The Primary endpoint for groups 1 and 2 (i.e., proportion of patients randomized to alpelisib with a confirmed objective response) used the same definition of responder used across all the studies (at least 20% reduction from baseline in the sum of target lesion volumes, provided that none of the individual target lesions has ≥ 20% increase from baseline and in absence of progression of non-target lesions and without new lesions).

The primary analysis was planned to be conducted when all patients completed the 48-week treatment period. As all patients were receiving alpelisib, comparisons with an internal, valid control were not possible.

The 16-week, placebo-controlled period was used to evaluate some secondary endpoints. However, considering the progressive, long-term nature of the disease, the short duration of this period seems insufficient to observe meaningful differences between alpelisib and placebo.

Secondary clinical endpoints include pain, overall clinical response as assessed by Investigator, change in PROS-related symptoms and complications/comorbidities, frequency of healthcare visits/hospitalizations due to PROS. The applicant did not use an endpoint specific to a symptom other than pain, which is acceptable in this case, considering the heterogeneity of symptoms in PROS disease. Clinical outcomes are considered critical to demonstrate the clinical relevance of the observed tumour reduction. However, given that sub-sequent to week 16, all patients receive alpelisib, the interpretability of these results may be challenging.

Statistical methods

The estimand framework is briefly described for the primary endpoint of Group 1 and Group 2. Within this framework, the applicant identifies two potential intercurrent events: 1) discontinuation of treatment prior to confirmation of response and 2) surgery as rescue therapy for any PROS lesions (target or other). Both intercurrent events are imputed as non-responders. A similar approach has been followed for the key secondary endpoint. This approach is acceptable.

The planned analyses, populations of interest, and sub-group analyses are described in the documentation provided by the applicant, and no concerns are identified.

Regarding the sample size, calculations were based on Groups 1 and 2 of this study. Specifically, the applicant justified their assumptions using data from Venot et al 2018, Adams et al 2016, Parker et al 2019 and the previous study EPIK-P1. A total of 78 patients were planned to be randomised at a ratio of 2:1, since 52 patients were required to test the hypothesis of a confirmed response rate of ≥35%, with a 1-sided alpha of 1.25% and 86% power for each group. Additionally, simulations were provided to estimate the probability of success for either of the two primary endpoints, as well as for the key secondary endpoint in the comparative stage of the trial. The operating characteristics of the design are clearly presented. Therefore, the sample size assumptions are considered acceptable based on the information available at the time of study design.

Protocol amendments

Important protocol amendments were implemented after the study had already started. The study began on 19/04/2021, and the first amendment was made on 14/01/2022 (with 43 patients enrolled at that time). This amendment included a number of changes such as revisions to the primary endpoint hypothesis, sample size, secondary endpoints, and the addition of Group 4. Amendment 2 dated 28/09/2022 (110 patients enrolled), included further changes: the modification of the primary endpoint, the addition of new secondary endpoints and the inclusion of Group 5. Amendment 3 dated 11/04/2023

(177 patients enrolled) added a new exclusion criterion. Lastly, Amendment 4 dated 05/10/2023 (by which time enrolment in Groups 1, 2, and 4 had been completed), included major revisions: change of the primary analysis timing (from 24 to 48 weeks) and the revision of the durability assessment for confirmed objective response (from 42 to 48 months). These amendments should be considered in the context of the DCO, which was 25/09/2024.

Despite the significant impact of the first amendment, the motivation for these changes was based on the results obtained from the EPIK-P1 study at that time, and all related elements were updated accordingly. The rationale behind Amendment 2 was linked to the accelerated approval granted by the FDA. Amendment 3, which introduced a new exclusion criterion, was implemented following a DMC meeting after the death of a participant. This change aimed to strengthen the 16th existing exclusion criterion. The rationale for the first three amendments is considered acceptable from a regulatory perspective, and no concerns are raised, including the changes introduced in Amendment 3, despite the high level of recruitment maturity at that point.

However, the potential impact of changing the timing of the primary endpoint and the assessment of response durability introduced in Amendment 4 was uncertain. This amendment was implemented late in the study (just one year before the DCO) after all participants from the main groups had already been recruited.

The applicant justifies the change based on a pooled, blinded review of EPIK-2 data conducted in preparation for a DMC meeting. The high frequency of dose escalations in Groups 1 and 2, where most participants required one or even two dose increases, was cited as the main reason for the amendment. However, the study design itself allowed for multiple dose escalations during Period 2, a design decision made by the applicant. Furthermore, both the primary endpoint and the secondary endpoint on response durability are assessed during a phase where all patients are evaluated in a single-arm context, making changes to their timing particularly sensitive.

Modifying a primary endpoint after full randomisation is inherently problematic. While the rationale provided is acknowledged, the risk of bias and the potential threat to study integrity are substantial. The applicant states that the change to the primary endpoint did not affect the FWER, thereby avoiding any undesirable inflation of the type I error rate and provided the simulation analyses mentioned to support this conclusion, suggesting no change or modest.

Efficacy data and additional analyses

EPIK-1

As previously stated, this study was pivotal in the previous application and no new data has been provided with this submission.

At cut-off date (9 March 2020) a total of 58 patients were eligible for inclusion in the study; one of whom withdrew consent prior to data collection. Of the 57 patients treated, 52 patients (91.2%) continued to receive alpelisib as of the data cut-off date, while five patients (8.8%) had discontinued study treatment. Reasons for discontinuation included "Subject decision" in three patients (5.3%), "Physician decision" (due to multiple AEs of mild to moderate severity) for one patient (1.8%), and "Other" (defined as "No efficiency") in one patient (1.8%).

Most of the patients were paediatric patients (39 patients 68.4%) including 11 patients aged 2 to 6 years old. No elderly patients were included. The median age of all patients was 14 years (range: 2 to 50 years). The demographic characteristics of the population is considered acceptable in view of the indication applied for.

57.9% of the patients were female (33 patients).

The most reported sub-type of PROS was Congenital lipomatosis overgrowth, vascular malformation, epidermal nevi and scoliosis/skeletal/spinal anomalies CLOVES (42 patients, 73.7 %) followed by megalencephaly capillary malformation polymicrogyria (MCAP) (8 patients 14%), Klippel-Trenaunay syndrome (KTS) (5 patients 8.8%), and facial infiltrating lipomatosis (FIL) (3 patients 5.3%).

Results Primary endpoint

The primary endpoint was evaluated on the complete cases population (i.e. patients with at least one target lesion and an imaging scan performed on the index date or up to 24 weeks prior to the index date) for at least one target lesion i.e. a total of 32 out of 57 treated patients fulfilled inclusion criteria.

Overall, the proportion of patients with response at Week 24 (± 4 weeks) was 37.5% (12/32 patients) with 95% CI: 21.1; 56.3 based on ICRR.

However, the interpretation of the proportion of response is challenging due to the retrospective open label design of the study and the absence of external control, natural history study or historical data.

Sub-group analysis

The rate of responders was the same between male and female patients in the complete case setting.

All 12 patients who responded to treatment had CLOVES, no patients were considered responders in the other PROS sub-types.

Although it was planned in the protocol, no information was collected by the applicant on the type of target lesions selected by the IRRC, i.e., if limited to vascular tissue lesions or if non-vascular soft tissue lesions were also selected for some patients. Therefore, no sub-group analyses were conducted on the effect of treatment by tissue type, but rather by the anatomical location site. This limitation adds further uncertainty to whether some benefit could be expected across the broad spectrum of PROS and patients regardless of the type of tissue affected.

In the complete cases setting, the response rate was higher in the adult population (5/9 patients, 55.6%, 95% CI 21.2; 86.3) than in the paediatric population (7/23 patients, 30.4%, 95%CI: 13.2; 52.9). The following are the proportion of patients achieving a response within the paediatric population, according to age: 2/7 (28.6%) in the age group 2-5 years, 1/7 (14.3%) in the age group 6-11 years and 4/9 (44.4%) in the age group 12-18 years. Even if the numbers are low, the proportion of responders in paediatric patients associated with the absence of proper dose ranging study raises the question of the appropriateness of the chosen dose in this group.

Results Secondary endpoints

The observed responses appeared durable among the 12 patients with a response, although the median DoR was not estimable as no events (progression or death) were reported at the time of the data cut-off date. Median time to censoring was 63.3 weeks (range 1 day, 187 weeks).

A total of 23 out of 31 (74.2%) patients had any reduction in the sum of target lesion volume. The rate of patients who had a reduction in the sum of target lesion volume was higher in the adult population 8/9 patients (88.8%) than in the paediatric population 15/22 patients (68.2%).

The mean percentage change at Week 24, in the sum of target lesion volume, as assessed by ICRR was -13.66%; -19.69% in the adult population and -11.20% in the paediatric population.

As with the responder rate, the mean volume reduction and the number of patients who had a reduction in the volume of the target tumours were higher in the adult population than in the paediatric population

Concomitant PROS-related medications

Treatment with alpelisib was associated with reduction in the use of concomitant medications to manage PROS (index date: 34/57 patients, 59.6%; Week 24: 30/56, 53.6%; end of study 25/57 patients, 43.9%).

However, the treatment was associated with the use of concomitant medications to treat alpelisib complications (index date: 0/57 patients 0%, week 24: 5/57 patients 8.9%; end of study 7/57 patients (12.3%). Concomitant medications included treatment for hyperglycaemia, alopecia and mouth stomatitis (see safety evaluation).

The number of patients receiving PROS-related non-drug treatments remained stable in the full population during the course of treatment with alpelisib.

Changes in PROS symptoms and complications

In the Full study population, the most reported PROS-related signs and symptoms at the index date were fatigue, vascular malformation, limb asymmetry, disseminated intravascular coagulation, and pain.

The severity of signs /symptoms was reported using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and improvement was defined based on at least one severity grade reduction or resolution of the signs and symptoms, considering the full study population.

An improvement was reported at Week 24 in the 5 most reported PROS-related signs and symptoms in most patients (from 50% to 91%), the improvement was consistent across age groups.

A reduction in the number of grade 3/4 PROS-related signs and symptoms was also observed at Week 12, at Week 24, and subsequently sustained and/or improved until the end of study.

PROS related signs and symptoms were abstracted retrospectively from the patient medical chart, no questionnaires or scales were used, which may generate biases.

Regarding pain severity, a questionnaire was collected in 11 patients. Among them only 6 had data at the index date and Week 24. All remained stable with no pain.

EPIK-P3

Of the 52 patients who completed EPIK-P1, 48 patients were enrolled in EPIK-P3 and none discontinued treatment during the retrospective period. Of the 48 patients who completed the retrospective period, 40 patients were enrolled in the prospective period.

Overall, the EPIK-P3 results showed that most patients stabilized or improved both the overall clinical and lesion condition since the start of treatment, with stabilisation in most representative PROS-related sign and symptoms sustained with long-term treatment, as perceived by the treating physician. However, these results should be interpreted with caution given that these patients represent the most favourable selected subset within the total treated population of patients previously included in EPIK-P1, i.e. those with perceived benefit from and who tolerated treatment. In addition, there was a lack of standardisation in the follow up and patients' evaluation for efficacy and safety, which were based on the subjective assessment of the treating physician.

In addition to signs/symptoms stabilization/improvement, a reduction on the need for surgeries is considered a clinically meaningful outcome. Following initiation of alpelisib (during EPIK-P1) to the end of the retrospective period in EPIK-P3, 3 pediatric patients had surgeries due to disease progression. No adult had surgeries due to disease progression. In order to provide some context for these results, the Applicant stated that prior to pre-index period of EPIK-P1 (from the time of their diagnosis), 50 patients had had at least 1 surgery due to disease progression. However, this information should be interpreted carefully, since the duration of both time periods (from confirmed diagnosis to inclusion in EPIK-P1 and the duration of the retrospective phases of EPIK-P1+P3) are not comparable (e.g., median time from diagnosis to inclusion in EPIK-P1 was 25.5 years for adults and 10.0 years for pediatric patients; median duration of alpelisib exposure for the retrospective portions of EPIK-P1+P3: 42.0 months [range: 3.4-74.8 months]).

EPIK-P2

Although this study included 5 different groups, the primary analysis of this study concerned the outcomes of Groups 1 and 2 at 48 weeks. In fact, only Group 2 paediatric cohort (aged 6 to 17 years) initiated treatment at a dose of 50 mg once daily in line with the claimed dosage in this application, while the dosage tested in Group 1 adult cohort and in Group 5 paediatric cohort are different from those claimed in this appliation. Furthermore, paediatric Groups 3, 4 and 5 are exploratory.

The proportion of patients with severe/life-threatening PROS that was actually included in this study was not initially provided. The Applicant developed a post-hoc algorithm that showed that the majority of paediatric participants in EPIK-P2 were classified as having non-severe PROS at baseline. These findings question the applicability of the results from EPIK-P2 to the intended severe PROS claimed indication. Furthermore, major shortcomings are identified for the algorithm: the robustness of the components is not equally distributed, and prospective validation is lacking.

The FAS for Groups 1 and 2 included 81 adult patients (54 in alpelisib group, 27 in the placebo group) and 84 paediatric patients (56 in alpelisib group, 28 in the placebo group), respectively.

The majority of patients that participated in the initial 48-weeks of EPIK-P2 continued into the extension 2 part of the study (65 (80.2%) and 78 (92.9%), in groups 1 and 2, respectively), which is still ongoing. The main reasons for discontinuation, at any time in the study, were "subject/guardian's decision" (9.9% and 3.6%, in groups 1 and 2, respectively), followed by "adverse events" (4.9% and 2.4%).

It is noted that most of the responders at week 48 had already responded at week 24 (16.7% and 19.6%). Moreover, no patients in the placebo arms responded during the first 16-week period and 1 patient assigned to placebo in group 2 responded by week 24 (already receiving alpelisib from week 16 onwards).

Group 2 (6-17 years 50 mg q.d.)

Both arms were well balanced regarding demographics and disease characteristics. Median age was similar between the 2 arms (10.9 years in the alpelisib arm vs 9.9 in the placebo arm), younger patients were assigned to the placebo group (67.9% were between 6-11 years old), than the alpelisib group (50% 6-11, 50% 12-17), but the overall numbers are too small; the majority of patients were female ((51.8% in the alpelisib arm vs 57.1% in the placebo arm). PROS phenotypes represented half of the patients, around 22.7% had ILM/lymphatic malformations and 11.9% KTS; the other phenotypes were more anecdotal. Approximately 2/3 of patients in each group had one of the mutations labelled as "frequent" (64.4% and 69.0%, respectively).

Response rate after all randomized patients reached 48 weeks of treatment or discontinued (primary analysis) showed that 13 out of 56 patients were responders, leading to an overall response rate (ORR)

of 23.2% (97.5% CI: 11.9–38.3). Further, the proportion of responders is considered modest and the clinical relevance itself is questionable.

It is noted that most of the responders at week 48 had already responded at week 24 (16.7% and 19.6%). Moreover, no patients in the placebo arms responded during the first 16-week period and 1 patient assigned to placebo in group 2 responded by week 24 (already receiving alpelisib from week 16 onwards).

Dose escalation was permitted for therapeutic optimisation after week 25 and 85.4% of paediatric patients had at least one dose increase. These findings raise concerns regarding the appropriateness of the proposed dosing regimen for patients aged between 6 to 18 years. Study (EPIK-P4), an open-label, non-controlled study is currently evaluating a 125 mg starting dose in paediatric patients aged 6 to 17 years with a shorter dose escalation window. Depending on the results, these findings could enable the currently recommended starting dose to be adjusted in order to further optimise treatment outcomes in this population.

The median duration of response was not estimable with a median follow-up of 55.1 weeks at the DCO date. Of the 13 responders 2 had progressive disease, 1 patient progressed at Week 40, but was assessed as a responder again at Weeks 72 and 96 and another patient experienced disease progression at Week 96.

Regarding overall clinical response, the majority of patients at week 16 demonstrated either clinical improvement or stability in the same range in both alpelisib and placebo arm. At Week 48, an increased proportion of patients demonstrated clinical improvement however, the observed increase in the proportion of patients demonstrating clinical improvement between Week 16 and Week 48 is subject to significant methodological limitations as the evaluation physician was aware of treatment allocation.

Among the patients with BPI worst pain intensity score assessment at baseline, the mean average weekly pain intensity score was similar across treatment arms and remained stable up to Week 16 in the alpelisib arm and increased in the placebo arm. However, results should be interpreted with caution due to the small sample size.

Group 4 (2-5 years 50 mg q.d)

Seven patients were enrolled (median age: 3.0 years; range: 2–5). The most common PROS phenotypes were CLOVES (57.1%) and isolated lymphatic malformations. At Week 24, 28.6% (2/7) of patients achieved a confirmed response per BIRC; this decreased to 14.3% at Week 48. All six patients in Group 4 with data at Week 24 showed a reduction in target lesion volume; the mean change at Week 48 was -16.5% (SD: 33.13). Clinical response was either improved or stable in all patients at both timepoints. However, interpretation of these findings is limited by the exploratory nature of the study, the small sample size, and the absence of a comparator arm.

Group 5 (6-17 years 125 mg q.d.)

The starting dose for paediatric patients in Group 5 (i.e., 125 mg) is higher than the starting dose recommended within the current application. Sixteen patients, with a median age of 9 years (range 6-17 years were enrolled, up to the DCO date, 14/16 (87.5%) patients completed 24 weeks or discontinued and 4/16 (25%) patients completed 48 weeks. The proportion of patients with confirmed response was 18.8% (3/16 patients) and the mean (SD) percentage change from baseline in the sum of target lesion volume was -7.9% (16.41) at Week 24 higher than in group 2.

The Applicant conducted an indirect comparison between Groups 2 and 5 to assess whether initiating treatment at a higher dose (125 mg in Group 5) leads to a higher response rate than starting at a lower

dose (50 mg in Group 2). The technical details are clearly documented in the SAP where the use of IPTW based on propensity scores to adjust for baseline characteristics are described. However, due to the small sample size in Group 5, the interpretability of this comparison is limited. This makes it difficult to achieve reliable adjustments for baseline characteristics and limits the robustness of the comparison. While the main analysis (and sensitivity analyses) suggests no major differences in response between the two groups, the strength of this conclusion is weakened by the methodological constraints of the analysis.

With regard to the sub-groups analyses, it appears that certain types of lesions and/or phenotypes respond better to alpelisib. However, given the limited sample sizes within each sub-group and the exploratory nature of these analyses, these findings need to be taken cautiously and definitive conclusions cannot be drawn.

Updated data Cut-of date Sep 2024 (6 months of additional follow-up).

Group 2

Compared to the primary analysis there is 1 additional confirmed responder following dose escalation. The proportion of patients randomized to alpelisib with a confirmed objective response was 25.0% (14/56 patients; 97.5% CI: 13.2, 40.3).

The median duration of response was estimated to be 28 months (95% CI: 11.1, NE) with a median follow-up of 16.9 months at the DCO date. Of the 14 patients with confirmed response, 3 had progressive disease and 1 patient needed rescue surgery, however, all 4 patients remained on treatment.

Group 1 (adult 125 mg q.d.)

The study did not neither meet its primary efficacy endpoint in the adult cohort initiating treatment at a dose of 125 mg once daily (Group 1) where, 9 out of 54 patients were responders, corresponding to an ORR of 16.7% (97.5% CI: 7.0–31.1). The failure to meet the primary endpoint in the adult population may be attributed to the sub-therapeutic starting dose compared to that proposed in the label. The results are in line the same range as those observed in the group 2, which questions the relevance of the proposed dose for the paediatric population. Dose escalation was permitted for therapeutic optimisation after week 25 and 72.5% of patients had at least one dose increase.

Group 4

The proportion of patients who achieved confirmed responder status remained unchanged from the primary analysis (2/7 patients; 28.6%).

Group 5

The proportion of patients with confirmed objective response is 25.0% (4/16 patients) with 95% CI: 7.3 to 52.4.

During the procedure, the applicant provided further data from an interim analysis for EPIK-P2 (cut-off 18-Feb-2025) with ~10 additional months of follow-up compared to the primary analysis.

In group 2 (paediatric population aged 6 to 18 years old), 3 new confirmed responses were achieved after dose escalation in the alpelisib arm; the response rate at the new interim analysis is 28.6%, (97.5% CI: 16%-44.1%). Among the 16 responders, 9 (56.3%) radiological responses were achieved at

the initial dose of 50 mg, and 7 (27.3%) following escalation to either 125 mg (2 patients) or 200 mg (5 patients) showing overall the importance of the dose optimization.

The median duration of response was estimated to be 121.6 weeks (95% CI: 82.3, NE) with a median follow up of 78.2 weeks. Four patients had progressive disease, and 1 needed rescue surgery, but all remained on treatment. Overall clinical response at the new cut-off date was 46.4% of patients compared to in 42.9% in the previous analysis. Additionally, 2 new confirmed responses were also observed in the placebo arm after switching to alpelisib.

New confirmed responses (3) were also observed in group 1 (adult population) however considering that the starting dose does not correspond to that claimed in the label, the relevance of those data is limited.

Special population

Elderly patients

One patient over the age of 40 was included in the EPIK P1, 17 were included in EPIK-P2 and 97 were treated in the MAP. The oldest of these patients was 62 years old. The absence of data in patients aged 65 years and above is refected in the SmPC.

Observational data

Managed Access Program (MAP)

A MAP was set-up by the Applicant and covered the period from 11-Jan-2016 (the date of first treatment under the ATU) to 31-AUG-2025 (the cut-off date for this analysis). A total of 945 patients with diagnosis of PROS that was severe or life-threatening and preferably evidence of a mutation in the PIK3CA gene were included in a total of 36 countries

The median age of patients was 13 years (range: 0-79); 618 were paediatric patients (median age: 8 years) and 327 were adult patients (median age: 31 years, range 18-79 years). In majority of patients (59.2%), PROS disorder type not specified.

The median dose requested for paediatric patients was 50 mg (range: 20-250 mg) and 250 mg (range: 50-300 mg) for adult patients.

No formal efficacy evaluation was performed. Using the resupply requests as surrogate measure, the estimated overall median duration of treatment was 17.7 months (17.9 months for paediatric patients and 16.9 months for adult patients).

Real-world evidence (RWE) platform, AllStripes

The Applicant provided data from an RWE platform that collected lesion assessments and occurrence of surgery from 40 patients from US, Canada and the UK with genetic diagnosis of PROS. At the time of diagnosis, 31 patients (77.5%) were pediatric, and 9 (22.5%) were adults.

Among the 40 patients, the most prevalent PROS sub-type was CLOVES, observed in 20 cases (50.0%). Other sub-types included Klippel-Trenaunay syndrome (KTS) in 5 patients (12.5%), Fibroadipose Hyperplasia or Overgrowth in 5 patients (12.5%), CLAPO syndrome in 1 patient (2.5%), and Facial Infiltrating Lipomatosis in 1 patient (2.5%). The PROS sub-type was not reported for 12 patients (30.0%).

All patients underwent lesion assessment performed by their physicians, with 31 patients (77.5%) exhibiting at least one instance of disease progression. Additionally, all 40 patients had undergone at least one surgical procedure, and 30 patients (75.0%) had undergone more than two surgeries. The median number of surgical interventions per patient was 6, with a range spanning from 1 to 22 procedures.

The limited patient sample size, coupled with variations in clinical management practices—both geographically and temporally, may compromise the generalizability of the findings to the broader PROS population. Moreover, the lack of clarity regarding patient selection criteria and the methodologies employed for lesion assessment data collection introduce uncertainty about the reliability of the data and the representativeness of the cohort relative to the overall PROS population.

5.3.7.2. Conclusions on the clinical efficacy

The current application is mainly based on the EPIK-P1 study, a retrospective chart review that included a total of 57 patients treated in the context of a compassionate use program, although the primary analysis (i.e., response at week 24) was conducted on the complete case sub-population, which was comprised of 32 patients.

Treatment with alpelisib was associated with reduction in the use of concomitant medications to manage PROS (index date: 34/57 patients, 59.6%; Week 24: 30/56, 53.6%; end of study 25/57 patients, 43.9%) in the full population. At Week 24, an improvement was reported in the majority of patients for the 5 most reported PROS-related signs and symptoms (fatigue, vascular malformation, limb asymmetry, disseminated intravascular coagulation, and pain). The improvement was consistent across age groups in the full population.

Concerns regarding the reliability and robustness of results from the pivotal trial are raised due to the retrospective chart review design, the simple size and the lack of standardisation of the clinical outcomes collection. The applicant provided details/clarifications on the mitigation measures implemented to address the concerns derived from the retrospective nature of the EPIK-P1 study. The open label design and the sameple size could be understood in view of the severity and the rarity of the disease.

With regards to EPIK-P3, of the 52 patients who terminated EPIK-P1, 48 patients were enrolled in EPIK-P3 and none discontinued treatment during the retrospective period. Of the 48 patients who terminated the retrospective period, 40 patients (31 paediatric and 9 adults) were enrolled in the prospective period.

The EPIK-P3 results showed that most patients had improved (9/40 [22.5%]) or stable (29/40 [72.5%]) overall lesion response during the first 12 months of the prospective period compared to the previous assessment and stabilisation in most representative PROS-related signs and symptoms sustained with long-term treatment. The EPIK-P3 data would support the benefit of alpelisib treatment in the long term, with a benefit demonstrated and attributed to the treatment with alpelisib. However these results need to be interpreted with caution given that the 40 patients included represent the most favourable selected subset of the 58 patients of EPIK P1, i.e. those who perceived benefit from treatment. In addition, there was a lack of standardisation in the follow-up and patients' evaluation for efficacy.

Additionally, the Applicant provided supportive data from an initial 16-week, randomized, double-blind, placebo-controlled period study, that aimed to assess efficacy of alpelisib in patients with symptomatic or evolutive overgrowth PROS irrespective of disease severity (EPIK-P2).

The proportion of patients with confirmed response after all patients reached week 48 or discontinued was 23.2% (13/56) in the paediatric population even if the primary objective was not met.

At the end of the placebo-controlled period (week 16), the proportions of patients with response in the alpelisib arm were 11.1% (6/54) in the adult group and 8.9% (5/56) in the paediatric group versus no responses in the placebo arms.

With update from an interim analysis with a later cut-off (18-Feb-2025), 3 new confirmed responses were achieved after dose escalation in the alpelisib arm (response rate of 28.6%, (97.5% CI: 16%-44.1%)) and 2 new confirmed in the placebo arm after switching to alpelisib were observed in the paediatric group. Overall clinical response showed either clinical improvement or stability in the majority of patients at week 16 and an increased proportion of patients demonstrated clinical improvement at Week 48.

However limitations are derived from the design of the study, including i) a short duration of the double-blind period (16 weeks) that does not allow for a proper characterization of the effect within the confines of a placebo-controlled setting; ii) the inclusion of a broader population than the target population, which compromises the external validity of the results; iii) the selection of a different dosing regimen (for adults) than the one intended for marketing, and iv) the comparison versus placebo was a secondary endpoint of the study that cannot be formally tested due to the failed primary analysis.

The precise effect of alpelisib on the progression of PROS is unclear, as no relevant data were provided on the natural rate of the disease progression prior to treatment initiation, nor were submitted natural history studies or relevant bibliographic data.

During the procedure the CHMP consulted with clinical experts in the framework on an Ad Hoc experts' group (AHEG) (see section 9.6.3.2). Clinical experts indicated that no spontaneous regression in PROS is expected and that the lesions would most likely progress in the absence of any intervention, and therefore the effect observed in the studies is most likely attributed to alpelisib, in particular as no other treatment was administered.

Besides, even if no definitive correlation has been established between lesion volume reduction and clinical outcomes, a positive trend was observed in the improvement of PROS related symptoms, and as highlighted by the AHEG, the radiologic response should not be the only parameter to quantify the response to treatment in PROS patients considering the range of lesions presentations including some where even a minimal change of volume could be significant for patients. Clinicians indeed highlighted that a clinical improvement could be observed in patients despite very limited reduction of the lesions' volume and that these responses have to be considered in the context of improved clinical outcomes that vary across patients given the heterogeneity of the disease manifestations.

In addition, there is a mechanistic rationale supporting the use of alpelisib in the treatment of PIK3CA-Related Overgrowth Spectrum (PROS). Activating mutations in the PIK3CA gene result in hyperactivation of the PI3K/AKT/mTOR signalling pathway, leading to the development of heterogeneous segmental mosaic overgrowth disorders collectively known as PROS. Alpelisib is a an α-specific PI3K inhibitor which has demonstrated clinical benefit in solid tumours (notably breast cancer), as well as activity in both in vitro and in vivo non-clinical models of PROS. Available data, including the ICRR review, suggest that the tumour reduction observed in some patients with PROS are attributable to treatment with alpelisib.

Overall, taking into account the rarity of the disease, the severity of the indication applied for, the unmet medical need in the PROS setting, the mecanistic plausibility, the clinicians views and considering the observed response rate in the context of improved clinical outcomes in the clinical studies, the efficacy of alpelisib in patients with sevre PROS can be considered established in the framework of a conditional MA.

As part of their obligation in the context of a conditional MA, the applicant will submit the results of a Phase II single arm, open-label, multi-center study to confirm the efficacy and safety of alpelisib in paediatric and adult patients with PROS.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The evaluation of alpelisib safety profile is maily based on the three clinical studies: EPIK-P1, EPIK-P3 and EPIK-P2.

▪ EPIK-P1 is a completed retrospective study, designed to assess the safety and efficacy of alpelisib for the treatment of patients (n= 57, 39 pediatric patients between 2- 17 years, and 18 adult patients aged ≥ 18 years) with severe or life-threatening manifestations of PROS;

▪ EPIK-P3 was designed to evaluate the long-term safety and efficacy of alpelisib in patients with PROS who previously participated in EPIK-P1 and who continued to receive treatment with alpelisib after the EPIK-P1 data cut-off date (i.e. 09-Mar-2020). Forty-eight (n=48) patients (34 pediatric patients between 2- 17 years, and 14 adult patients aged ≥ 18 years). The study had a completed retrospective period and a subsequent ongoing prospective period.

The Applicant has pooled safety data from both studies EPIK-P1 and EPIK-P3 since data in EPIK-P1 and the retrospective period of EPIK-P3 were collected from the same patients. Retrospectively collected data were combined or "pooled" to provide a comprehensive view of the patient journey from the start of EPIK-P1 to the end of the retrospective period of EPIK-P3. It is agreed that safety data from EPIK-P1 study and from the retrospective period of EPIK-P3 can be pooled.

▪ EPIK-P2 is a phase II, multicenter study with an upfront, 16-week randomized, double-blind, placebo-controlled period, to assess the efficacy, safety, and pharmacokinetics (PK) of alpelisib in pediatric and adult patients with PROS (n= 188 patients with PROS). This double-blind period is followed by two extension periods: from week 25 to week 48, and an ongoing long-term treatment up to 5 years. Five groups have been designed one with adult patients (group 1, n=81, treated with orally alpelisib 125 mg QD) and 4 groups with pediatric patients with different age groups and different dosage of alpelisib. Group 2 enrolled 84 pediatric patients aged between 6-17 years and receiving alpelisib 50 mg QD, group 4 is an exploratory group, and enrolled 7 pediatric patients aged between 2- 5 years treated with alpelisib 50 mg QD, and, group 5 enrolled 16 pediatric patients aged between 6-17 years treated with alpelisib at a higher alpelisib starting dose i.e.125 mg QD. Group 3 will enrol pediatric patients aged between 2-5 years old receiving alpelisib with granules and is expected to start in Q2-2025.

The data presented in this report from EPIK-P2 focuses on that collected in pediatric patients 2 to 17 years of age treated with alpelisib 50 mg starting dose that is recommended in the proposed alpelisib SmPC (i.e. orally 50 mg QD).

Furthermore, due to different study design and posology, the Applicant did not pool and compare safety data from EPIK-P2 with those observed in EPIK-P1 and EPIK-P3 studies.

5.4.2. Patient exposure

As mentioned above, safety data were obtained from all patients who participated in EPIK-P1 and entered the retrospective period of EPIK-P3 and from the paediatric patients group from EPIK-P2 study who received alpelisib 50 mg starting dose that is recommended in the proposed alpelisib SmPC.

▪ EPIK-P1 and EPIK-P3 pooled data

For all 57 patients who participated in EPIK-P1 (39 paediatric patients and 18 adult patients), the median duration of exposure to alpelisib from the start of alpelisib in EPIK-P1 up to the last exposure in EPIK-P1 or the retrospective period of EPIK-P3 was 42.0 months (range: 3.4-74.8 months).

The median duration of exposure to alpelisib was 43.3 months (range: 3.4-64.4 months) in the paediatric population (<18 years at the start of EPIK-P1), and 40.5 months (range: 12.2-74.8 months) in the adult patients. Eleven (28.2%) paediatric and 2 (11.1%) adult patients had an exposure duration of >60 months. The median average daily dose was 50.0 mg (range: 50.0 to 250.0 mg) in paediatric patients and 250.0 mg (range: 79.1 to 250.0 mg) in adult patients.

▪ EPIK-P2 – group 2

The recommended starting dose for alpelisib was 50 mg FCT q.d., p.o. with food in Group 2. Patients who were randomized to the placebo arm initially received placebo during the 16-week placebo-controlled period of the study and ongoing patients were subsequently transitioned to treatment with alpelisib during the alpelisib period.

Placebo-controlled period

In Group 2, the median duration of exposure for patients randomized to the alpelisib arm (16.1 weeks; range: 14.0 to 18.9 weeks) was similar to the median duration of exposure for patients in the placebo arm (16.0 weeks; range: 0.7 to 23.7 weeks). The median average daily dose was 50.0 mg (range: 50.0 to 51.0 mg) for the alpelisib arm and 50.0 mg (range: 50.0 to 50.0 mg) for the placebo arm.

Alpelisib period

In Group 2, after Week 16, 26/28 patients switched from placebo to alpelisib. The recommended starting dose for alpelisib was 50 mg FCT q.d. orally with food. As of the 25-Sep-2024 cut-off date, the median duration of exposure to alpelisib was 26.4 months (range: 4.9 to 40.5 months). At the time of data cut off, 32.9% of patients in Group 2 had a duration of exposure of at least 22 months (96 weeks). The median average daily dose received was 105.6 mg (range: 50.0 to 206.0 mg). For 82 patients included, 80 patients were exposed to alpelisib treatment for >72 weeks (~17 months).

5.4.3. Adverse events

5.4.3.1 Common treatment emergent adverse events (TEAEs)

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3

Table 43 presents an overview of TEAEs in EPIK-P1 and EPIK-P3 retrospective pooled data and, as supportive data, TEAEs from EPIK-P3 1-year prospective period:

Table 45 Summary of adverse events EPIK-P1 and EPIK-P3 retrospective pooled data and EPIK-P3 1-year prospective period

	EPIK-P1 and EPIK-P3 retrospective pooled data				**EPIK-P3 1-year prospective period**			
	Paediatric patients (2-17 years) N=39		**Adult patients (≥ 18 years) N=18**		**Paediatric patients (2-17 years) __N=31__**		**Adult patients (≥ 18 years) __N=9__**	
Category	**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	35 (89.7)	11 (28.2)	18 (100)	11 (61.1)	7 (22.6)	3 (9.7)	4 (44.4)	2 (22.2)
Treatment-related	11 (28.2)	0	13 (72.2)	1 (5.6)	3 (9.7)	0	2 (22.2)	0
SAEs	12 (30.8)	6 (15.4)	12 (66.7)	10 (55.6)	3 (9.7)	3 (9.7)	2 (22.2)	2 (22.2)
Treatment-related	0	0	3 (16.7)	1 (5.6)	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0	0	0
AEs leading to dose reduction	0	0	3 (16.7)	0	0	0	0	0
Treatment-related	0	0	1 (5.6)	0	1 (3.2)	0	0	0
AEs leading to dose interruption	2 (5.1)	0	4 (22.2)	2 (11.1)	1 (3.2)	0	0	0
Treatment-related	1 (2.6)	0	3 (16.7)	1 (5.6)	0	0	0	0

Numbers (n) represent the counts of patients. Number (N) represents the total number of patients included in the analysis.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version 4.03. (EPIK-P1 and EPIK-P3 Pooled data)
All grades includes any AEs with missing grade.
Source: BYL719 PROS SCS-Table 2-1; BYL719 PROS SCS-Table 2-2

▪ EPIK-P2 study-group 2

Table 44 presents an overview of TEAEs in EPIK-P2, group 2 (patients between 6 – 17 years):

Table 46: Summary of adverse events in EPIK-P2 placebo-controlled period and alpelisib period

	Group 2 (6 - 17yrs)				
	Placebo-controlled period		Alpelisib period		
	Alpelisib arm N=56	Placebo arm N=28	Alpelisib arm N=56 n (%)	Alpelisib Placebo arm N=26 n (%)	All paediatrics N=82 n (%)
Adverse events	**50 (89.3)**	**24 (85.7)**	**55 (98.2)**	**26 (100)**	**81 (98.8)**
Treatment-related	19 (33.9)	9 (32.1)	37 (66.1)	17 (65.4)	54 (65.9)
AEs with grade ≥3	7 (12.5)	2 (7.1)	18 (32.1)	6 (23.1)	24 (29.3)
Treatment-related	3 (5.4)	0	8 (14.3)	2 (7.7)	10 (12.2)
SAEs	3 (5.4)	2 (7.1)	12 (21.4)	3 (11.5)	15 (18.3)
Treatment-related	1 (1.8)	0	5 (8.9)	1 (3.8)	6 (7.3)
Fatal SAEs	0	1 (3.6)	0	0	0
Treatment-related	0	0	0	0	0
AEs leading to discontinuation	0	0	1 (1.8)	1 (3.8)	2 (2.4)
Treatment-related	0	0	1 (1.8)	1 (3.8)	2 (2.4)
AEs leading to dose adjustment/interruption	4 (7.1)	4 (14.3)	16 (28.6)	5 (19.2)	21 (25.6)
AEs leading to dose reduction	0	0	2 (3.6)	1 (3.8)	3 (3.7)
AEs leading to dose interruption	4 (7.1)	4 (14.3)	15 (26.8)	5 (19.2)	20 (24.4)
AEs requiring additional therapy	43 (76.8)	15 (53.6)	51 (91.1)	18 (69.2)	69 (84.1)

5.4.3.2 Adverse events by preferred term (PT)

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3

The most common AEs (≥10% incidence in any column) by PT reported in the pool of EPIK-P1 /EPIK-P3 retrospective period and the supportive EPIK-P3 1-year prospective period, are summarized in the Table 45 :

Table 47: Overall summary of adverse events (≥10% incidence in any column), regardless of drug relationship, by preferred term across the pool of EPIK-P1 and the EPIK-P3 retrospective period, the EPIK-P3 1-year prospective period,

	EPIK-P1 and EPIK-P3 pooled data		EPIK-P3: 1-year prospective period	
	Paediatric	Adult	Paediatric	Adult
	N = 39	N = 18	N = 31	N = 9
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients with at least one event	35 (89.7)	18 (100.0)	7 (22.6)	4 (44.4)
Diarrhoea	5 (12.8)	5 (27.8)	0	0
Headache	0	4 (22.2)	0	0
Pyrexia	0	0	1 (3.2)	0
Abdominal pain	0	0	0	0
COVID-19	6 (15.4)	0	4 (12.9)	2 (22.2)
Alopecia	0	3 (16.7)	2 (6.5)	0
Nasopharyngitis	0	0	0	0
Pain in extremity	1 (2.6)	3 (16.7)	0	0
Vomiting	1 (2.6)	1 (5.6)	1 (3.2)	0
Nausea	1 (2.6)	2(11.1)	0	0
Fatigue	3 (7.7)	1 (5.6)	0	0
Decreased appetite	0	0	0	0
Cough	0	0	1 (3.2)	0
Oropharyngeal pain	0	0	1 (3.2)	0
Upper respiratory tract infection	0	0	0	0
Influenza	0	0	0	0
Aphthous ulcer	6 (15.4)	3 (16.7)	0	0
Abdominal pain upper	0	0	0	0
Dry skin	2 (5.1)	2 (11.1)	0	0
Hyperglycaemia	3 (7.7)	5 (27.8)	0	0
Inflammation	5 (12.8)	2 (11.1)	0	0
Eczema	1 (2.6)	3 (16.7)	0	0
Vascular malformation	4 (10.3)	3 (16.7)	0	0
Cellulitis	1 (2.6)	2 (11.1)	1 (3.2)	0
Hypoglycaemia	4 (10.3)	0	0	0
Gait disturbance	2 (5.1)	2 (11.1)	0	0
Disseminated intravascular coagulation	2 (5.1)	3 (16.7)	0	0

▪ EPIK-P2 study - group 2

Placebo-controlled period

The most common AEs (≥5% incidence in any column) by PT reported in the EPIK-P2 Group 2 (patient between 6- 17 years) are summarized in the Table 46:

Table 48 Adverse events (at least 5% incidence of patients in either arm), regardless of study drug relationship, by preferred term and severity – Placebo-controlled period (Safety set) – EPIK-P2

Preferred term	_____ Group 2 (6 - 17yrs) _____ Alpelisib arm N=56 All grades n (%)	Grade ≥ 3 n (%)	Placebo arm N=26 All grades n (%)	Grade ≥ 3 n (%)
Number of participants with at least one event	50 (89.3)	7 (12.5)	24 (85.7)	2 (7.1)
Diarrhoea	5 (8.9)	0	3 (10.7)	0
Headache	11 (19.6)	0	3 (10.7)	0
COVID-19	10 (17.9)	1 (1.8)	3 (10.7)	0
Abdominal pain	5 (8.9)	0	2 (7.1)	0
Nausea	5 (8.9)	0	2 (7.1)	0
Fatigue	5 (8.9)	0	3 (10.7)	0
Nasopharyngitis	4 (7.1)	0	4 (14.3)	0
Cough	4 (7.1)	0	1 (3.6)	0
Decreased appetite	4 (7.1)	0	1 (3.6)	0
Pyrexia	5 (8.9)	1 (1.8)	1 (3.6)	0
Vomiting	6 (10.7)	0	2 (7.1)	0
Abdominal pain upper	3 (5.4)	0	1 (3.6)	0
Influenza	3 (5.4)	0	2 (7.1)	0
Oropharyngeal pain	6 (10.7)	0	0	0
Upper respiratory tract infection	5 (8.9)	0	1 (3.6)	0
Toothache	3 (5.4)	0	0	0
Anxiety	0	0	2 (7.1)	1 (3.6)
Pruritus	0	0	3 (10.7)	0
Epistaxis	0	0	2 (7.1)	0

Alpelisib period

The most common AEs (≥5% incidence in any column) by PT reported in the EPIK-P2 Group 2 (patient between 6- 17 years) are summarized in theTable 47:

Table 49: Summary of adverse events (at least 5% incidence in all patients), regardless of study drug relationship, by preferred term and severity – EPIKP2 Group 2

Preferred term	_____Group 6- 17 Alpelisib (Alpelisib arm) N=56 All grades n (%)	Grade ≥ 3 n (%)	Alpelisib (Placebo arm) N=26 All grades n (%)	Grade ≥ 3 n (%)	_____ All pediatrics N=82 All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	55 (98.2)	18 (32.1)	26 (100)	6 (23.1)	81 (98.8)	24 (29.3)
Diarrhea	16 (28.6)	1 (1.8)	6 (23.1)	0	22 (26.8)	1 (1.2)
Alopecia	6 (10.7)	0	2 (7.7)	0	8 (9.8)	0

Headache	20 (35.7)	0	5 (19.2)	0	25 (30.5)	0
Abdominal pain	15 (26.8)	0	8 (30.8)	0	23 (28.0)	0
COVID-19	14 (25.0)	1 (1.8)	2 (7.7)	0	16 (19.5)	1 (1.2)
Pyrexia	17 (30.4)	1 (1.8)	8 (30.8)	0	25 (30.5)	1 (1.2)
Pain in extremity	13 (23.2)	3 (5.4)	4 (15.4)	0	17 (20.7)	3 (3.7)
Nasopharyngitis	9 (16.1)	0	8 (30.8)	0	17 (20.7)	0
Vomiting	12 (21.4)	0	7 (26.9)	0	19 (23.2)	0
Nausea	9 (16.1)	0	3 (11.5)	0	12 (14.6)	0
Fatigue	8 (14.3)	0	2 (7.7)	0	10 (12.2)	0
Cough	7 (12.5)	0	2 (7.7)	0	9 (11.0)	0
Decreased appetite	6 (10.7)	0	1 (3.8)	1 (3.8)	7 (8.5)	1 (1.2)
Influenza	7 (12.5)	0	3 (11.5)	0	10 (12.2)	0
Oropharyngeal pain	9 (16.1)	0	2 (7.7)	0	11 (13.4)	0
Rash	7 (12.5)	0	0	0	7 (8.5)	0
Upper respiratory tract infection	9 (16.1)	0	2 (7.7)	0	11 (13.4)	0
Abdominal pain upper	8 (14.3)	0	2 (7.7)	0	10 (12.2)	0
Gastroenteritis	3 (5.4)	0	2 (7.7)	0	5 (6.1)	0
Inflammation	4 (7.1)	1 (1.8)	2 (7.7)	0	6 (7.3)	1 (1.2)
Eczema	4 (7.1)	0	3 (11.5)	0	7 (8.5)	0
Mouth ulceration	4 (7.1)	0	2 (7.7)	0	6 (7.3)	0
Toothache	6 (10.7)	1 (1.8)	2 (7.7)	0	8 (9.8)	1 (1.2)

5.4.3.1. Adverse drug reactions

Table 48 summurises the ADRs proposed for inclusion in section 4.8 of the SmPC.

Table 50: Summary of ADRs proposed for inclusion in the SmPC

Adverse drug reactions	**EPIK-P1 and EPIK-P3* retrospective period pooled data**		**EPIK-P2[1]**	**Highest frequency category across adult and paediatric patients**	**Rationale for inclusion**
	Adult patients N = 18	**Paediatric patients N = 39**	**Paediatric patients[2] N = 89**		
	All grades n (%)	**All grades n (%)**	**All grades n (%)**		
Immune system disorders					
Hypersensitivity[#]	-	-	-	Common	AESI. Treatment-related AEs, requiring dose interruption, were reported in PROS patients treated with alpelisib (outside of the EPIK-P1/EPIK-P2/EPIK-P3 safety population). Known ADR in the oncology setting.
Metabolism and nutrition disorders					

Hyperglycaemia[3]	5 (27.8)	3 (7.7)	6 (6.7)	Very common	AESI, on target effect of PIK3CA inhibition. Treatment-related AEs reported in EPIK-P1/EPIK-P3 and EPIK-P2 studies.
Decreased appetite	1 (5.6)	0	10 (11.2)	Very common	Treatment-related AEs were reported in PROS patients. Known ADR in the oncology setting.
Dehydration	1 (5.6)	1 (2.6)	-	Common	Known ADR in the oncology setting. Other known ADRs, such as nausea, vomiting, and hyperglycaemia, may cause dehydration.
Nervous system disorders					
Headache	4 (22.2)	0	27 (30.3)	Very common	Treatment-related AEs were reported in PROS patients, often in the first 2-3 weeks of treatment. Known ADR in the oncology setting.
Gastrointestinal disorders					
Diarrhoea	5 (27.8)	5 (12.8)	25 (28.1)	Very common	AESI. Frequently reported in PROS patients. Known ADR in the oncology setting.
Vomiting	1 (5.6)	1 (2.6)	22 (24.7)	Very common	AESI. Treatment-related AEs were reported in PROS patients. Known ADR in the oncology setting.
Stomatitis[4]	3 (16.7)	9 (23.1)	17 (19.1)	Very common	AESI. Frequently reported in PROS patients. Known ADR in the oncology setting.
Nausea	2 (11.1)	1 (2.6)	15 (16.9)	Very common	AESI. Frequently reported in PROS patients. Known ADR in the oncology setting.
Abdominal pain	1 (5.6)	0	30 (33.7)	Very common	Frequently reported in PROS patients. Known ADR in the oncology setting.
Skin and subcutaneous tissue disorders					
Rash[5]	-	-	10 (11.2)	Very common	AESI. Frequently reported in PROS patients. Known ADR in the oncology setting.
Dermatitis[6]	3 (16.7)	1 (2.6)	12 (13.5)	Very common	Frequently reported in PROS patients. Skin reactions (incl. rash, acne, dermatitis acneiform) are frequent with alpelisib, and some features overlap.
Dry skin	3 (16.7)	2 (5.1)	3 (3.4)	Very common	Treatment-related AEs were reported in PROS patients. Known ADR in the oncology setting.
Alopecia[7]	3 (16.7)	0	11 (12.4)	Very common	AESI. Frequently reported in PROS patients. Known ADR in the oncology setting.
Acne[8]	1 (5.6)	0	4 (4.5)	Common	Skin reactions (incl. rash, acne, dermatitis acneiform) are frequent with alpelisib, and some features overlap.
Pruritus	0	1 (2.6)	2 (2.2)	Common	It may be a symptom of other skin reactions caused by alpelisib. Known ADR in the oncology setting.
General disorders and administration site conditions					
Mucosal dryness[9]	1 (5.6)	1 (2.6)	2 (2.2)	Common	It includes dry mouth, which may be a symptom of

					hyperglycaemia. Known ADR in the oncology setting.
Investigations[10]					
Blood phosphate decreased	11 (61.1)	27 (69.2)	2 (2.2)	Very common	Repeated post-baseline decreases, mostly of mild (Grade 1) severity, were noted in several patients in EPIK-P1/EPIK-P3 safety population.
Blood calcium decreased[11,12]	12 (66.7)	25 (64.1)	17 (19.1)	Very common	Post-baseline decreases, mostly of mild (Grade 1) severity, were noted in several patients. Known ADR in the oncology setting.
Blood creatinine increased	2 (11.1)	19 (48.7)	22 (24.7)	Very common	Post-baseline increases, mostly of mild (Grade 1) severity, were noted in several patients. Known ADR in the oncology setting.
Glycosylated haemoglobin increased[12]	12 (66.7)	11 (28.2)	5 (5.6)	Very common	On target effect of PIK3CA inhibition.
Glucose increased[13]	4 (22.3)	8 (20.5)	27 (30.3)	Very common	On target effect of PIK3CA inhibition.
Lipase increased[14]	-	-	22 (24.7)	Very common	Grade 3 increases resolving after dose interruption were reported in EPIK-P2. Known ADR in the oncology setting.

Grading according to CTCAE Version 4.03.

[1]EPIK-P2 data refers to the alpelisib-treatment period which includes paediatric patients who received at least one dose of alpelisib, including patients who switched from placebo to alpelisib after the 16-week placebo-controlled period.

[2]All paediatric patients 2 to <18 years of age enrolled in EPIK-P2 and treated with Vijoice 50 mg tablets.

[3]Hyperglycaemia: including hyperglycaemia, glycosylated haemoglobin increased and blood glucose increased.

[4]Stomatitis: including stomatitis, aphthous ulcer and mouth ulceration.

[5]Rash: including rash, rash erythematous, rash macular, rash maculo-papular and rash papular. Rash was reported in 13.8% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

[6]Dermatitis: including dermatitis, drug eruption and eczema.

[7]Alopecia: Alopecia was reported in 36.3% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

[8]Acne: including acne and dermatitis acneiform.

[9]Mucosal dryness: including dry mouth and vulvovaginal dryness.

[10]Frequencies of laboratory terms reflect the proportion of patients who experienced worst-post-baseline laboratory measurements.

[11]Calcium corrected values were used for this parameter.

[12]No CTCAE grading available.

[13]Glucose increased is an expected laboratory abnormality of PI3K inhibition.

[14]Lipase increased was reported in 23.8% of adult patients treated at the non-recommended alpelisib dose of 125 mg in EPIK-P2.

* Forty patients in EPIK-P3 continued to be treated with alpelisib in a prospective period. Additional safety data from the 3-year analysis of the EPIK-P3 prospective period, with an additional median duration of exposure of 39.1 months (range: 17-42 months) did not show additional ADRs or clinically relevant laboratory abnormalities.

#Adverse drug reactions reported outside of the EPIK-P1/EPIK-P2/EPIK-P3 safety population considered. The frequency category is estimated from the EPIK-P2 study as per the SmPC Guideline 2009 section 4.8, *Adverse reactions from spontaneous reporting.*

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

5.4.4.1. Adverse events of special interest (AESIs)

The AESIs selected for alpelisib, aligned with those in the oncology setting, were GI toxicity (nausea, vomiting, diarrhoea), hyperglycaemia, alopecia, hypersensitivity, severe cutaneous reactions, rash, stomatitis, pneumonitis, and pancreatitis (Table 49):

Table 51 Summary of adverse events of special interest in the pool of EPIK-P1 and the EPIK-P3 retrospective period and the EPIK-P2 placebo-controlled period and alpelisib period– Safety set

	EPIK-P1 and EPIKP3 pooled data		**EPIK-P2 Placebo-controlled period**	**EPIK-P2 Alpelisib period**
AESI category	**Paediatric N = 39 n (%)**	**Adult N = 18 n (%)**	**Paediatric N = 84 n (%)**	**Paediatric N = 82 n (%)**
GI toxicity (nausea, vomiting, diarrhoea)	6 (15.4)	7 (38.9)	18 (21.4)	35 (42.2)
Alopecia	0	3 (16.7)	1 (1.2)	11 (13.4)
Stomatitis	9 (23.1)	3 (16.7)	1 (1.2)	13 (15.9)
Rash	1 (2.6)	0	5 (6.0)	13 (15.9)
Hyperglycaemia	3 (7.7)	5 (27.8)	0	6 (7.3)
Pancreatitis	0	0	0	3 (3.7)
Hypersensitivity	4 (10.3)	4 (22.2)	1 (1.2)	15 (18.3)
Pneumonitis	1 (2.6)	0	0	0
Severe cutaneous adverse reactions	0	1 (5.6)	0	0

5.4.4.2. Serious adverse events (SAEs)

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3

Among all patients, SAEs were experienced by 24 patients (42.1%). The majority of SAEs were not attributed to alpelisib, but to the underlying or concurrent conditions of patients with PROS. SAEs suspected to be treatment-related were experienced by 3 patients (5.3%), all of whom were adults. One adult patient experienced a grade ≥ 3 SAE of cellulitis which was assessed by the investigator as suspected to be treatment related. None of the pediatric patients experienced a SAE considered to be treatment related.

▪ EPIK-P2 study - group 2

Placebo-controlled period: the incidence of SAEs in pediatric patients was low in both the alpelisib arm (3 patients, 5.4%) and the placebo arm (2 patients, 7.1%). SAEs that were reported in the alpelisib arm

included: ashtma, COVID-19 and infection. All individual SAEs were reported as single cases in both arms. One treatment-related SAE reported in alpelisib arm was infection.

Alpelisib period: the incidence of individual SAEs was low among pediatric patients; 15 patients (18.3%) had at least one SAE and 9 patients (11.0%) had Grade ≥ 3 SAEs and most frequent (≥ 2 patients) was cellulitis and growth retardation. SAEs assessed as suspected to be study treatment related by the investigators were reported in 6 patients (7.3%), and Grade ≥ 3 SAEs in 5 (6.1%) patients. The most frequent (≥ 2 patients) SAE considered to be related to study treatment was growth retardation (2 patients, 2.4%).

5.4.4.3. Deaths

No deaths were reported in patients treated with alpelisib in EPIK-P1 and EPIK-P3 retrospective and prospective period. In EPIK-P2 study, one paediatric patient in the group 2 who was randomized to placebo arm died on Day 5 due to massive embolisms in multiple locations and haemolytic streptococcal group A infection.

5.4.5. Discontinuation due to adverse events, interruption and dose adjustment due to adverse events

5.4.5.1. Adverse events leading to dose discontinuation

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3: Neither paediatric nor adult patients had ADRs leading to dose discontinuation.

▪ EPIK-P2 study - group 2: No ADRs leading to discontinuation were reported in paediatric patients in the placebo-controlled period. However, during the alpelisib period, there was 1 patient (1.1%) with an AE of alopecia and 1 patient (1.1%) with an AE of decreased appetite (grade ≥3 event) leading to dose discontinuation in the alpelisib period.

5.4.5.2. Adverse events leading to dose interruption

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3:

AEs leading to dose interruption were experienced by 6 patients (10.5%). Two patients (3.5%) experienced a Grade ≥3 AE leading to dose interruption. In pediatric patients, AEs leading to dose interruption were experienced by 5.1% pediatric patients and included vomiting, viral infection, burn of internal organs, acidosis, dehydration, dizziness, and lethargy. No pediatric patient experienced a Grade ≥3 AE leading to dose interruption.

In adult patient, AEs leading to dose interruption were experienced by 22.2% adult patients and included dizziness, vomiting, AGEP, cellulitis, headache, impaired healing, libido decreased, menstruation irregular, nausea, urinary tract infection and vulvovaginal dryness. Two adult patients experienced a Grade ≥3 AE leading to dose interruption.

▪ EPIK-P2 study - group 2

During the placebo-controlled period, AEs leading to dose interruption were experienced by 7.1% pediatric patients in alpelisib arm and 14.3% in the placebo arm. AEs leading to dose interruption were: pyrexia, COVID-19, infection, influenza, varicella, procedural pain and pharyngeal disorder (n=1 each).

During the alpelisib period, AEs leading to dose interruption were experienced by 24.4% patients (26.8% in alpelisib arm and 19.2% in the placebo arm). Grade ≥ 3 AEs leading to dose interruption were reported in 11% patients. AEs leading to dose interruption reported were: pyrexia (n=4), vomiting (n=3), diarrhea, growth retardation, inflammation, viral infection, influenza, and rash (n=2, each). Grade ≥ 3 AE leading to dose interruption reported in > 2 patients was growth retardation (n=2).

5.4.5.3. Adverse events leading to dose reduction or adjustment

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3

No AEs leading to dose reductions occurred in pediatric patients. AEs leading to dose reduction were experienced by 3 adult patients (5.3%). One patient each experienced alopecia, memory impairment, and soft tissue infection, none of which were grade ≥ 3 AEs.

In the prospective period of EPIK-P3 study, dose reduction was observed in 1 pediatric patient (3.2%) due to a grade 1 AE of Alopecia. The dose was reduced for 2 days but was subsequently re-escalated. The event required additional medication (bepanthene) and was assessed by the investigator to be treatment-related.

▪ EPIK-P2 study - group 2

There were no dose reductions due to AEs during the placebo-controlled period in group 2

Dose reduction due to AEs occurred in 3 patients during the alpelisib period. Two were due to AEs of growth retardation and one due to an AE of ketonuria.

5.4.6. Safety in special populations

6.4.6.1 Intrinsic factors

Sub-group analysis for the impact of gender, race and region on safety profile based on current EPIK-P1 data were not conducted due to the small number of patients in these categories.

Sub-groups for the effect of age, race and gender on safety profile were performed based on patients with breast cancer in SOLAR-1. Safety evaluation in special populations with renal impairment and hepatic impairment are reflected in section 4.2 of the SmPC for Vijoice.

No dedicated study in patients with renal impairment or in patients with moderate or severe hepatic impairment were done for this application. Analyses were conducted for the breast cancer indication.

6.4.6.1 Extrinsic factors

Use in pregnancy, fertility and lactation

There were no pregnancies and lactating related events reported in the alpelisib clinical development program. Pregnant and lactating women were excluded of the clinical trial. Studies in animals have shown reproductive toxicity (embryotoxic, foetotoxic and teratogenic) and fertility adverse effects. In

addition, mechanistic rationale (PI3 kinase inhibitors) suggests reproductive and developmental toxicity.

Overdose, drug abuse, withdrawal and rebund, effects on ability to drive and use machine

There is limited experience of overdose with alpelisib in clinical studies. No new information about abuse/dependence potential, withdrawal and rebund, and effects of alpelisib on ability to drive or operate machinery or impairment of mental ability, has been generated in support of this application.

5.4.7. Safety related to drug-drug interactions and other interactions

No data on drug interactions were generated in EPIK-P1, EPIK-P3 retrospective- and prospective period, and EPIK-P2.

5.4.8. Vital signs and laboratory findings

5.4.8.1. Vital signs

The vital signs, physical findings, and other observations related to safety reported in EPIK-P3 and EPIK-P2 did not reveal any new concern. Generally, these results are consistent with those reported in EPIK-P1 and support the consistency of the safety profile of alpelisib in patients with PROS (see clinical AR).

Serial, triplicate 12 lead ECGs were collected to evaluate the effect of alpelisib on QT prolongation in patients with PROS in EPIK-P2 and EPIK-P3. No clinically significant QT prolongation was observed at doses up to 250 mg daily under fed conditions.

Treatment with alpelisib appeared to have no impact on the growth and pubertal development of pediatric patients with respect to long-term data from the EPIK-P1 and retrospective period of EPIK-P3 pool and EPIK-P3, 1-year prospective period. The treatment duration in EPIK-P2 is currently insufficient to determine whether alpelisib has an adverse impact on growth and development in pediatric patients with PROS.

5.4.8.2. Laboratory findings

Hematology

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3:

The most frequently reported haematological abnormalities were: decreased hemoglobin (43.6% pediatric patients and 27.8% adult patients), decreased lymphocytes (41% pediatric patients and 22.2% adult patients), increased lymphocytes (2.6% pediatric patients), decreased leukocytes (43.6% pediatric patients and 27.8% adult patients), decreased neutrophils (28.2% pediatric patients and 5.6% adult patients), decreased platelets (20.5% pediatric patients and 27.8%adult patients). There were mainly grade 1 and grade 2. No Grade 3 hematological abnormalities were reported in adult population during the retrospective period whilst one pediatric patient experienced grade 3 hematology abnormality. An 18-year-old patient 5640-093) who had an isolated Grade 3 decrease of neutrophils at Week 140. This event was preceded by normal neutrophil counts and was not considered by the Investigator as clinically significant. No grade 4 events were reported.

▪ EPIK-P2 study - group 2:

Hematology abnormalities from the EPIK-P2 study group 2 were consistent with those seen in EPIK P3 retrospective period. Most of these hematologic abnormalities were grade 1 or 2.

Clinical chemistry

▪ Pool EPIK-P1 and the retrospective period of EPIK-P3:

The following worst-post baseline biochemistry abnormalities (≥ 25% all patients) observed were: calcium corrected decrease (64.1% pediatric patient and 66.7% adult patients), AST increase (38.5% pediatric patient and 33.3% adult patient), ALT increase (25.6% pediatric patients and 27.8% adult patients), creatine kinase increase (33.3% pediatric patient and 44.4% adult patients), bilirubin increase (25% pediatric patients and 50% adult patients), creatinine increase (48.7% pediatric patient), increased cholesterol (33.3% pediatric patients) and GGT increase (38.9% adult patients).

Increased bilirubin was grade 3 clinical chemistry abnormality reported in a 5-year-old pediatric patient at Week 239. The event was preceded by grade 1 increased bilirubin at Week 173, which was reported as an AE. The outcome of the event was not resolved before the end of the retrospective period, and it was assessed by the investigator as not treatment-related.

One grade 3 magnesium increase was also reported in pediatric patient. Likewise, grade 3/4 clinical chemistry abnormalities were reported in one adult patient. The corresponding patient was a [2-55]-year-old and had increased urate (Grade 4) from Week 228 to Week 294. The event was accompanied by increased creatine kinase (Grade 4) at Week 294, and increased creatinine (Grade 3) from Week 272 to Week 305. The patient was affected by chronic kidney dysfunction from [****], as well as chronic nephrotic range proteinuria from [****], which explain the observed values.

▪ EPIK-P2 group 2:

During the placebo-controlled period of the study were mainly mild-to-moderate in severity. The most frequently reported (≥ 25% in either arm) worst-post baseline biochemistry abnormalities in the alpelisib arm compared to placebo arm were creatinine clearance decreased (30.4% vs. 14.3%) and, creatine kinase increased (25.0% vs. 17.9%). One patient in alpelisib arm experienced grade ≥3 worst post baseline biochemistry abnormalities. It was an event of creatine kinase increased the narrative of which has not been found.

During the alpelisib period, the common worst-post baseline biochemistry abnormalities (≥ 25% all patients) included increased magnesium (65.9%), decreased creatinine clearance (58.5%), increased creatine kinase (50.0%), and increased cholesterol (40.2%). Grade ≥ 3 worst post baseline biochemistry abnormalities in Group 2 were: creatine kinase increased (4 patients, 4.9%), cipase increased (3 patients, 3.7%) and ALT increased, AST increased, bilirubin increased, urate increased (1 patient, 1.2% each).

5.4.9. Post-marketing experience

Overall data from post-marketing surveillance and the review of SAEs retrieved from the Applicant Global Safety Database did not identify any new safety concerns compared to the currently known safety profile of alpelisib.

5.4.10. Overall discussion and conclusions on clinical safety

5.4.10.1. Discussion

5.4.10.1.1. Overall assessment of available safety data

The safety profile of alpelisib administered as monotherapy for the treatment of adult and paediatric patients aged 2 years and older with PROS, is based on safety data collected from 146 patients (18 adult and 128 paediatric) across 3 clinical studies: EPIK-P1 (pivotal study), EPIK-P3 and the supportive study EPIK-P2, as well as from patients treated under compassionate use programs and in the post-marketing setting in the US. Data from EPIK-P1 were submitted with the previous MAA in Jun-2022. As part of the current submission, new data from EPIK-P3 and EPIK-P2 have been provided.

EPIK-P1 study is a retrospective non-interventional medical chart review study performed with 57 PROS patients (39 paediatric patients from 2 to 17 years of age and 18 adult patients). The recommended starting dose was 50 mg daily for paediatric patients 2 to 17 years old and 250 mg daily for adult patients.

EPIK-P3 is an ongoing Phase II, multicenter, open-label study in patients who previously participated in EPIK-P1 and continued alpelisib treatment after the EPIK-P1 DCO date (09-Mar-2020). For patients who discontinued alpelisib after 09-Mar-2020, the retrospective period ended 30 days after the discontinuation of alpelisib.

The study comprised an initial retrospective period and a sub-sequent prospective period. The retrospective period has been completed. One-year prospective data were initially provided as new information as part of the current submission. During the procedure, updated data were submitted, including 3-year prospective data.

Data from EPIK-P1 and the retrospective period of EPIK-P3, collected from the same patients, were "pooled" to assess the safety of alpelisib. This pool includes data from all patients who enrolled in EPIK-P1 and data from those who subsequently enrolled in the retrospective period of EPIK-P3. The pool also includes patients who discontinued treatment in EPIK-P1 and those who did not participate in the retrospective period of EPIK-P3 for other reasons.

In the EPIK-P1 study and the subsequent follow-up in the retrospective period of EPIK-P3, 35/39 (89.7%) of the paediatric participants received the recommended starting dose of 50 mg for a total of 111.8 subject treatment years (STYs). All adult patients received the recommended starting dose of 250 mg for a total of 52.3 STYs.

EPIK-P2 in an ongoing Phase II double-blind study with an upfront 16-week randomized, placebo-controlled period, in adult patients (Group 1) and 6- to 17-year-old paediatric patients (Group 2) with PROS irrespective of disease severity. The study included also two exploratory groups of less than 6-year-old paediatric patients (Group 3 and Group 4) and an exploratory group of 6- to 17-year-old paediatric patients treated at a higher starting dose than Group 2 (Group 5).

In EPIK-P2, all pediatric participants in Group 2 received the recommended starting dose of 50 mg for a total of 68.6 STYs, whereas only 33/80 (41.3%) of the adult participants in Group 1 received the recommended starting dose of 250 mg for a total of 33 STYs.

Due to different study design and posology, the Applicant did not pool and compare safety data from EPIK-P2 with those observed in EPIK-P1 and EPIK-P3 studies.

EPIK-P1 and EPIK-P3 retrospective period pooled

Safety data were obtained from all patients who participated in EPIK-P1 and entered the retrospective period of EPIK-P3. Of the 48 patients enrolled in EPIK-P3, 34 were pediatric patients (70.8%) at the time of alpelisib initiation and 14 were adult patients (29.2%). As of the cut-off date for the retrospective period of EPIK-P3, all 48 patients were still receiving treatment with alpelisib.

Patient exposure (received at least 1 dose of active treatment)

The median duration of exposure to alpelisib from the start of alpelisib in EPIK-P1 (for all 57 patients who participated in EPIK-P1) up to the last exposure in EPIK-P1 or the retrospective period of EPIK-P3 was 42.0 months (43.3 months in the paediatric population and was 40.5 months in adult patients). In the EPIK-P3 retrospective period, the median duration of exposure was 24.6 months.

Adverse Events (AEs)

AEs (all grades) were reported in the majority patients in both adult (100%) and paediatric (89.7%) patients. Most of them were mild to moderate in severity. Serious AEs were reported in 66.7% adult patients whilst 30.8% in paediatric patients. No AEs led to drug discontinuation.

The most frequent AEs (> 15% of patients) in adults' patients were: diarrhoea, hyperglycaemia, headache, alopecia, pain in extremity, aphthous ulcer, eczema, vascular malformation and disseminated intravascular coagulation. In paediatric patients the most frequently reported AEs were COVID-19 and aphthous ulcer.

Treatment-related AEs (all grades) were reported in 11 (28.2%) paediatric patients and 13 (72.2%) adult patients. In all patients, the most frequent treatment-related AEs were aphthous ulcer and hyperglycaemia.

Grade ≥ 3 AEs were reported in 11 (28.2%) paediatric patients and in 11 (61.1%) adult patients.

Treatment-related Grade ≥ 3 AEs were reported only in one adult patient (5.6%).

Disseminated intravascular coagulation occurred in 5 patients (2 [5.1%] paediatric patients and 3 [16.7%] adult patients) and one of them was considered serious but none of them were considered related to alpelisib treatment and all the events recovered or were recovering. Almost half of patients in the EPIK-P1/EPIK-P3 presented DIC at baseline (29/57), of whom 16 (55.2%) recovered after starting treatment with alpelisib. DIC is considered a complication of PROS.

SAEs were reported in 24 patients (42.1%), in 12/39 (30.8%) paediatric and 12/18 (66.7%) adult patients. The most common SAEs (≥ 8% of patients) by SOC were: general disorders and administration site conditions (4 pediatric patients, 10.3%; 2 adult patients, 11.1%); infections and infestations (4 pediatric patients, 10.3%; 2 adult patients, 11.1%); injury, poisoning, and procedural complications (2 pediatric patients, 5.1%; 3 adult patients, 16.7%) and musculoskeletal and connective tissue disorders (1 pediatric patient, 2.6%; 4 adult patients, 22.2%).

SAEs suspected to be treatment-related were experienced by 3 patients (5.3%), all of whom were adults.

The adverse events of special interest (AESIs) selected for alpelisib were GI toxicity (nausea, vomiting, and diarrhoea), hyperglycaemia, alopecia, hypersensitivity, severe cutaneous reactions, rash, stomatitis, pneumonitis, and pancreatitis. AESIs from paediatric and adults' patients were respectively: GI toxicity (15.4% vs. 38.9%); alopecia (0 vs. 16.7%); stomatitis (23.1 vs. 16.7%); rash (2.6% vs. 0%); hyperglycaemia (7.7 vs. 27.8%); hypersensitivity (10.3 vs. 23.2%); one paediatric patient (2.6%) experienced an event of pneumonitis and one adult patient (5.6%) experienced an event of severe cutaneous adverse reactions (acute generalized exanthematous pustulosis). All AESI events were mild in severity (grade 1 or grade 2), except for 1 adult patient with grade 3 AESI of acute generalized exanthematous pustulosis. No such cases for severe hyperglycaemia events were found. No patient had an AESI of pancreatitis.

The overall assessment of adverse events of special interest with alpelisib is consistent with its mechanism of action as well as with its safety profile in the oncology indication. Gastro-intestinal toxicity (nausea, vomiting, diarrhoea, and stomatitis), hyperglycaemia, hypersensitivity, rash and alopecia are listed under the section 4.8 of the SmPC.

Even though no AESI of pneumonitis and severe cutaneous adverse reactions were observed during EPIK-P1 and EPIK-P3, they have been considered as AESI in PROS patients with a warning under the section 4.4 of the SmPC and in the RMP as important potential risks.

Discontinuation due to AEs: No patient had an AE which led to treatment discontinuation during the retrospective period for EPIK-P1 and EPIK-P3. In one (2.6%) paediatric patient and in 3 (16.7%) were treatment-related AESI, and in one adult patient (5.6%) was AE Grade ≥ 3 treatment-related. No AEs leading to dose reductions occurred in paediatric patients. In 3 adults' patients (16.7%) reporting AEs leading to dose reduction and in one patient (5.6%) was treatment-related. One patient each experienced alopecia, memory impairment, and soft tissue infection, none of which were grade ≥ 3 AEs.

Laboratory and other findings:

Laboratory abnormalities reported during the pooling period were mostly Grade 1 and Grade 2 and resolved without specific medical interventions.

In both paediatric and adult populations, haematological and clinical chemistry abnormalities reported during the pooling period were mostly Grade 1 and Grade 2. Grade 3 abnormalities were infrequent, and no Grade 4 abnormalities were reported. One event (PT of iron deficiency of Grade 2) was reported as an AE in a paediatric patient. The event was not related to study treatment and resolved.

However, in EPIK-P3 retrospective study, increased bilirubin grade 3 was reported in a 5-year-old paediatric patient at Week 239. The event was preceded by Grade 1 increased bilirubin at Week 173, which was reported as an AE. The outcome of the event was not resolved before the end of the retrospective period, and it was assessed by the investigator as not treatment-related. One grade 3 magnesium increase was also reported in a paediatric patient. The assessment of the corresponding narrative cannot allow a causal association with alpelisib treatment to be made based on the available data. Other confounding factors (underlying disease or condition) may have contributed.

Blood calcium decreased, blood phosphorus decreased, blood creatinine increased, glycosylated haemoglobin increased, lipase increased, and glucose increased were reported and listed under the section 4.8 of the SmPC.

EPIK-P3 1-year prospective period report

The full study population of the prospective period of EPIK-P3 consisted of 40 patients in total (31 pediatric patients (77.5%) and 9 adult patients (22.5%)). All 40 patients completed the first 12 months of treatment with alpelisib in the prospective period of the study, which is ongoing. The results from the 1-year analysis are based on the data cut-off date of 26-Aug-2023 (almost 2 years ago). Updated safety data for the prospective period of study EPIK-P3 were requested during the procedure and are also further detailed thereafter under the sub-section "Additional safety data".

Patient exposure

The median duration of exposure to alpelisib during the 1-year prospective period in EPIK-P3 for the overall population was 16.4 months. The median duration of overall exposure since the start of alpelisib in EPIK-P1 (for patients who participated in the prospective period of EPIK-P3) up to prospective period cut off data was 60.9 months and 60.6 months in the paediatrics and adults, respectively.

Adverse Events (AEs)

AEs (all grades) were reported in 44.4% of adult patients and in 22.2% of paediatric patients with most of the AEs being grade 1 or grade 2 in severity. The most frequent AEs by SOCs reported in ≥ 3 patients (7.5%) were infections and infestations (16.1% pediatric patients vs. 33.3% adult patients); respiratory, thoracic and mediastinal disorders (9.7% vs 0%) and skin and subcutaneous tissue disorders (9.7% vs. 0%). By preferred term, COVID-19 was the only AE reported in ≥ 3 patients (4 [12.9%] pediatric patients and 2 [22.2%] adult patients).

Treatment-related AEs (grade 1 or grade 2) were reported in 9.7% of paediatric patients and 22.2% of adult patients. Except for the PT of alopecia, which was reported in 2 patients (5.0%) (both pediatric), all other treatment-related AEs were reported in 1 patient (2.5%) each.

Grade ≥3 AEs were reported in 3 (9.7%) paediatric patients and in 2 (22.2%) adult patients. The grade 3 AEs by SOC reported in ≥ 2 patients (5.0%) were infections and infestations (2/31 pediatric patients, 6.5%; 1/9 adult patient, 11.1%), respiratory, thoracic, and mediastinal disorders (2/31 pediatric patients, 6.5%; 0 adult patients), and skin and subcutaneous tissue disorders (2/31 pediatric patients, 6.5%; 0 adult patients). No grade 4 AEs were reported and there were no treatment-related grade ≥ 3 AEs.

Patients in the EPIK-P3 1-year prospective period had received approximately 4 years of prior treatment with alpelisib before the study starts. During this prospective period, overall, the incidence of AEs decreased.

SAEs were experienced by 5 patients (12.5%) (3 pediatric patients, 9.7% and 2 adult patients, 22.2%). None of these SAEs occurred in more than one patient each. None of the SAEs were assessed to be treatment-related by the investigator.

The AESIs from paediatric and adults' patients were respectively: GI toxicity (nausea, vomiting, diarrhoea) (3.2% vs. 0%); alopecia (6.5 vs. 0%); rash (PT: Dermatitis psoriasiform) (3.2% vs. 0%); hyperglycaemia (0 vs. 11.1%); and hypersensitivity (PT: Dermatitis atopic) (3.2 vs. 0%). There was one pediatric patient (3.2%) that experienced GI toxicity (PT: vomiting), that was a grade 3 event. No patients had AESIs of stomatitis, severe cutaneous reactions, pneumonitis, or pancreatitis.

Discontinuation due to AEs: No patient had an AE which led to treatment discontinuation. None of the AEs led to dose interruption during the first 12 months. Dose reduction was observed in 1 paediatric patient (3.2%) due to a grade 1 AE of alopecia.

Laboratory and other findings

The haematological abnormalities reported were all grade 1 or 2, and none of them were considered clinically significant and did not require medical intervention. No grade 3 or 4 haematological abnormalities were reported.

The clinical chemistry abnormalities reported during the prospective period were mainly grade 1 or 2 in severity. Grade 3 and grade 4 clinical abnormalities were infrequent and none of these abnormalities were considered clinically significant.

EPIK-P2 study

The population enrolled in EPIK-P2 (i.e., patients with PROS irrespective of disease severity) is broader than that enrolled in EPIK-P1 and EPIK-P3 (i.e., patients with severe or life-threatening PROS). There were 5 groups to assess in the study: Group 1 (adult patients), Group 2 and 5 (paediatric patients 6 to 17 years old), and Group 3 and 4 (paediatric patients 2 to 5 years old). Groups 1, 2, 4, and 5 have completed enrollment. Eighty-one patients were enrolled in Group 1, 84 patients were enrolled in Group 2, 7 patients were enrolled in Group 4, and 16 patients in Group 5.

In EPIK-P2 study, 84 paediatric patients were randomized in the group 2 (6-17 years-old). Two patients did not pursue the study and did not receive alpelisib. They were initially randomized to placebo and discontinued treatment prior to the end of the placebo-controlled period. The reason of their discontinuation was not related to alpelisib. Therefore, 82 paediatric patients were included in the analysis.

Paediatric patients in Group 2 and exploratory Group 4 received alpelisib at a starting dose of 50 mg q.d., which is the proposed starting dose in the PI. Safety data from Group 2 and also exploratory data from group 4 were considered. However, adult patients in Group 1 and pediatric patients in Group 5 of EPIK-P2 were treated with a starting dose (125 mg q.d.) different from the recommended in the PI (i.e., 250 mg q.d.). Thus, safety data from Group 1 are not very informative considering the lower dose used.

Dose escalations for response optimization were permitted up to a maximum dose of 250 mg q.d. at 12-week intervals for all patients ≥ 6 years of age. In Group 1, 59 patients (73.8%) had at least one dose increase, with the most common reason being "physician's decision" (66.3%).

The primary analysis for this study was performed after all patients in Groups 1 and 2 had completed 48 weeks of study treatment or discontinued earlier. The results of this primary analysis are based on a data cut-off date of 20-Mar-2024. EPIK-P2 data were also analyzed with an additional cut-off of 25-Sep-2024 with approximately 6 months' additional follow-up in Groups 1, 2, 4 and 5. Updated safety data for EPIK-P2 study were requested during the procedure and are further detailed thereafter under the sub-section "Additional safety data".

Adverse events (AE)

The type of AEs reported in EPIK-P2 during the alpelisib period for pediatric patients was overall in line with the safety profile observed in patients with PROS treated with alpelisib in EPIK-P1/P3 studies. Of note, the incidence of AEs, SAEs, AESIs, AEs leading to discontinuation and AEs requiring dose adjustments/interruptions in these paediatric patients was less frequent than the reported in adult patients. According to the Applicant it may reflect the lower starting dose in this population (50 mg/day)

compared to adults (250 mg/day), which can be acknowledged since a higher exposure was observed in adult patients compared to paediatric patients.

Pancreatitis (AESI) was deemed to be treatment-related in 4 paediatric patients (4.5%), it resolved in 3 paediatric patients (3.4%), but 1 (1.1%) had an unresolved AE at the time of data cut-off.

The applicant was asked to further discuss cases of pancreatitis reported in paediatric and adult patients in EPIK-P2 and in the post marketing experience and whether pancreatitis should be considered an ADR of alpelisib. According to the applicant, only one case of pancreatitis (as preferred term) has been reported in EPIK-P2 in Group 1. This event was however not considered related to alpelisib. It is agreed that a clear association to alpelisib cannot be established. There were also 3 additional AEs under the AESI Pancreatitis: lipase increased (2) and amylase increased. Lipase increased is already included as ADR in the SmPC. No AEs of pancreatitis were reported in Group 2 of EPIK-P2 and EPIK-P1/EPIK-P3 studies. Among patients treated with alpelisib under the compassionate use programs and post-marketing experience 2 cases were reported (including the case reported above in the EPIK-P2 study). The other case was reported in the post-marketing setting in the US. In this patient other confounder factors were present since the patient has also cholelithiasis. In view of the reported data, the event should continue being monitored.

One of the main uncertainties identified during the assessment of data was the long-term safety of alpelisib and the effect of alpelisib on growth and development in the paediatric population, since no long-term, mature data were available. In the prospective trial EPIK-P2, 24 out of the 82 patients had at least one visit with a decrease below 2 or more percentile lines at some stage prior to the DCO date, of whom 17 patients had 2 or more visits in which this decrease was observed. AEs of growth retardation were reported in 6 patients, 4 of which were assessed as treatment-related by the Investigators. In 3 (3.4%) were AEs grade ≥3. The Applicant was asked to further discuss the potential effect of alpelisib on the growth retardation in paediatrics patients considering these results.

Hence, in the EPIK-P2 study 12 AEs of growth retardation were reported in paediatric patients, 3 of them considered as SAEs. According to the Applicant, all these events concerned slower longitudinal growth compared to the WHO growth charts, with 8 patients reporting a decrease ≥2 percentile lines. Bone age showed abnormalities in 4 patients although according to the Applicant they do not impact the overall bone development. Of these 12 AEs, 7 were considered related to alpelisib by the investigator. Looking at the depieced information provided by the Applicant, it is acknowledged that in several cases other confounder factors were present, which hampers establishing a causal relationship with alpelisib. Among the 3 SAEs, the issue was resolved or resolving in 2 cases and not resolved in the third one, which led to treatment discontinuation due to concerns about delayed growth. Regarding the remaining 9 non-SAEs, dose reductions were required in 3 patients (1 of them resolved) while no changes were made in the remaining 6 patients (only one resolved).

Further, 30 patients reported a decrease below ≥2 percentile lines (19 male and 11 female). Overall, no impact on pubertal maturation, bone age and development were observed, which is in some way reassuring.

In study EPIK-P3 two paediatric patients reported an AE of growth retardation. One of them had history of [Medical History] and [Medical History].

While some AEs regarding grow development have been observed in patients treated with alpelisib, in most cases it seems that this is not impacting the overall grow development. The treatment duration in EPIK-P2 is currently insufficient to determine whether alpelisib has an adverse impact on growth and development in paediatric patients with PROS and therefore, updated safety data are considered even more critical. Nevertheless, while it is not possible to unequivocally conclude on a causal relationship between alpelisib and grow development delay, due to the limitations of the safety dataset, a deleterious

impact cannot be ruled out either. Therefore, a statement is included in section 4.4 of the SmPC and section 2 of the PL to reflect the current evidence/lack of data on the long-term effect of alpelisib on growth and development in children. In addition, this concern is listed as missing information in the RMP.

In Group 1 of EPIK-P2 one patient randomized to alpelisib arm experienced a SAE of depression, suicidal ideation (grade 4). On Day 124, the study treatment (alpelisib, 125 mg) was permanently discontinued due to depression and suicidal ideation. Depression and suicidal ideation were assessed as suspected to be related to study treatment. Another patient randomized to placebo who switched to alpelisib experienced two episodes of a SAE grade 3 suicide attempt, although this was not considered related to the study treatment by the Investigator. In view of these events, the Applicant was requested to update the data on the risk of depression, suicidal ideation and suicide attempts associated with alpelisib in paediatric and adult patients, across all trials and post-marketing settings. Hence, the Applicant conducted a review of AEs reported under the following MedDRA HLGTs: 'Depressed mood disorders and disturbances' and 'Suicidal and self-injurious behaviours NEC'. In study EPIK-P2, according to the Applicant, no SAEs were reported in paediatric patients across Groups 2, 4 and 5. Four adult patients reported SAEs, one of them considered as related to alpelisib treatment. In these 4 cases other confounder factors were present, thus no conclusions can be drawn.

In EPIK-P1/EPIK-P3 no cases of depression, suicidal ideation or suicide attempts were reported.

Eight SAEs were reported in patients treated with alpelisib under the compassionate use programs and post-marketing, including the 4 cases from the EPIK-P2 study. In all cases, other confounder factors were also present. In addition to these SAEs, eight non serious AEs were reported in 7 patients, including depression (6) and depressed mod (1).

Therefore, considering the reported data, a causal relationship with alpelisib cannot be established, due to the presence of other confounder factors.

- **Group 2 EPIK-P2 Placebo-controlled period** (16-week period; DCO: 25 Sep 2024)

Patient exposure and disposition

The median duration of exposure for patients randomized to the alpelisib arm (56 patients) was 16.1 weeks and in the placebo arm (26 patients) was 16.0 weeks.

Two patients (2.4%) in the placebo arm (none in the alpelisib arm) discontinued treatment during the placebo-controlled period, one patient (1.2%) due to guardian decision and one patient (1.2%) due to death.

Adverse events (AEs)

AEs were experienced by 50 patients (89.3%) randomized to the alpelisib arm and 24 patients (85.7%) randomized to the placebo arm, which were considered treatment-related in 19 patients (33.9%) in the alpelisib arm and 9 patients (32.1%) in the placebo arm. Grade ≥ 3 AEs were 12.5% in the alpelisib arm vs. 7.1% in the placebo arm, and 3 patients (5.4%) in the alpelisib arm that had grade ≥ 3 AEs treatment related during the placebo-controlled period. No patient had AEs leading to discontinuation. There was 1 death in Group 2 in the placebo arm. AEs leading to dose adjustment/interruption occurred in 4 patients (7.1%) in the alpelisib arm and 4 patients (14.3%) in the placebo arm.

AEs by PT where there was a higher proportion of patients in the alpelisib arm reporting events (≥ 5% difference between the alpelisib arm and the placebo arm) were headache, COVID-19, oropharyngeal

pain, pyrexia, upper respiratory tract infection, and toothache. AEs by PT where there was a lower proportion of patients in the alpelisib arm reporting events (≥ 5% difference between the alpelisib arm and the placebo arm) were nasopharyngitis, pruritus, anxiety, and epistaxis.

SAEs were experienced by 3 patients (5.4%) in the alpelisib arm and 2 patients (7.1%) in the placebo arm during the placebo-controlled period. The most common SAEs (≥ 2 patients, 2.4%) by SOC in Group 2 was Infections and infestations, which occurred in 2 patients (3.6%) in the alpelisib arm and 1 patient (3.6%) in the placebo arm.

AESIs:

GI toxicity (nausea, vomiting, and diarrhea) was reported in 13 patients (23.2%) in the alpelisib arm and 5 patients (17.9%) in the placebo arm. No patients in Group 2 had a grade ≥ 3 GI toxicity.

Alopecia was reported in 1 patient (1.8%) in the alpelisib arm.

Stomatitis was reported in 5 patients (8.9%) in the alpelisib arm. No patients had grade ≥ 3 stomatitis. Rash was reported in 4 patients (7.1%) in the alpelisib arm and 1 patient (3.6%) in the placebo arm. No patients in Group 2 had a grade ≥ 3 Rash.

One patient (1.8%) in the alpelisib arm had an event of hypersensitivity.

No AESIs of hyperglycemia, pancreatitis, pneumonitis or severe cutaneous reactions were reported during the 16 weeks treatment period.

Discontinuation: No patient experienced an AE leading to treatment discontinuation. AEs leading to dose interruption were experienced by 4 patients, (7.1%) in the alpelisib arm and 4 patients (14.3%) in the placebo arm. The AEs leading to dose interruption by SOC were infections and infestations, gastrointestinal disorders, skin and subcutaneous tissue disorders, and injury, poisoning and procedural complications, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions. There were no dose reductions due to AEs during the placebo-controlled period.

Laboratory abnormalities

Most of the hematologic abnormalities in Group 2 were grade 1 or 2 and no trends were evident when comparing the alpelisib arm with the placebo arm. The most frequently reported (≥ 20% in either arm) worst-post baseline hematology abnormalities in the alpelisib vs. placebo arms were increased partial thromboplastin, neutrophils decreased, decreased blood leucocytes, and hemoglobin decreased.

Most of these biochemistry abnormalities were mild-to-moderate (grade 1 or 2) in Group 2, with no trends evident when comparing the alpelisib arm with the placebo arm. However, in the EPIK-P2 study, group 2, during the placebo-controlled period, one patient in alpelisib arm experienced grade ≥3 worst post baseline biochemistry abnormalities. The assessment of the narrative cannot allow a causal association to be made with alpelisib treatment, even though it occurred after alpelisib initiation, it resolved without any treatment change and may be explained by other confounding factors. Furthermore, based on results observed in EPIK-P2 study group 2, placebo-controlled period, it was observed that bilirubin, AST and ALT values increase in alpelisib arm whilst no event occurred in the placebo arm. However, the available data of the corresponding cases cannot allow a causal association with alpelisib to be established.

Group 2 EPIK-P2 Alpelisib period

Starting from Week 17, study treatment was administered in an open-label fashion and all patients received alpelisib. Safety data reported for the alpelisib period in EPIK-P2 have a DCO of 25-Sep-2024.

As of the 25-Sep-2024 cut-off date, the median duration of exposure to alpelisib was 26.4 months (range: 4.9 to 40.5 months). At the time of data cut off, 32.9% of all patients had a duration of exposure of at least 22 months (96 weeks). The median average daily dose received was 105.6 mg (range: 50.0 to 206.0 mg). Five patients (6.0%) in Group 2 discontinued treatment at the time of the data cut-off. There were 77 patients (91.7%) in Group 2 receiving ongoing treatment at the data cut-off date.

Adverse events (AEs)

AEs were experienced by 81 patients (98.8%), with AEs considered to be treatment related in most patients (65.9%). There were 24 patients (29.3%) that experienced a grade ≥ 3 AE, which was considered treatment related in 10 patients (12.2%). SAEs were reported for 15 patients (18.3%) that were treatment-related in 6 patients (7.3%), and AEs leading to discontinuation were reported for 2 patients (2.4%). AEs leading to dose adjustment/interruption were reported in 21 patients (25.6%), and AEs requiring additional therapy were reported in 69 patients (84.1%). The most frequently reported AEs by PT, irrespective of study drug relationship were headache (30.5%), pyrexia (30.5%), abdominal pain (20.7%), diarrhoea (26.8%), vomiting (23.2%), pain in extremity (20.7%), and nasopharyngitis (20.7%).

Treatment-related AEs: AEs suspected to be study drug related were reported in 54 patients (65.9%). The most frequent study drug related AEs by PT reported (in ≥ 5% of all patients) were headache (14.6%), diarrhea, abdominal pain (11.0% each), nausea (8.5%), alopecia (7.3%), and abdominal pain upper, fatigue, decreased appetite, mouth ulceration (6.1% each).

Nonetheless, in the EPIK-P2 study, during the alpelisib period, several adverse events were suspected related to alpelisib: COVID-19, nasopharyngitis, upper respiratory tract infections, influenza, pain in extremity and toothache. The Applicant further discussed these AEs and presently, albeit a temporal association with alpelisib treatment no causal association with alpelisib can be established. Other confounding factors may have contributed to these adverse events.

Grade ≥ 3 AEs occurring in at least 2 patients included pain in extremity and growth retardation (3.7%, each) and blood creatinine phosphokinase increased and lymphopenia (2.4%, each). There were 10 patients (12.2%) that had grade ≥ 3 AEs by PT that were suspected to be study treatment related during the alpelisib period; grade ≥ 3 AE of growth retardation suspected to be study treatment related occurred in 2 patients (2.4%). All other grade ≥ 3 AEs were reported in 1 patient only.

SAEs were experienced by 15 patients (18.3%) and 9 patients (11.0%) reported at least one grade ≥ 3 SAE. The most common SAEs (≥ 2 patients, 2.4%) by SOC were infections and infestations and musculoskeletal and connective tissue disorders.

AESIs: all grade AESIs reported were GI toxicities (nausea, diarrhea, vomiting) (42.7%), hypersensitivity (18.3%), stomatitis and rash (15.9% each), and alopecia (13.4%). Also reported hyperglycemia (7.3%), pancreatitis (3.7%), and was grade ≥ 3 in 1.8%. No pediatric patients experienced pneumonitis AESI or severe cutaneous reactions AESI in the alpelisib period.

Discontinuation: 2 patients (2.4%) experienced an AE leading to treatment discontinuation during the alpelisib period. AEs leading to dose interruption were experienced by 21 patients (25.6%) during the alpelisib period. Dose reduction due to AEs occurred in 3 patients (3.7%).

Laboratory abnormalities

Most of the hematologic abnormalities were grade 1 or 2.

Most of these biochemistry abnormalities were mild-to-moderate (grade 1 or 2) and were consistent with those seen in EPIK-P1 and EPIK-P3.

Exploratory Group 4 (n=7): patients 2-5 years of age treated at a starting dose of 50 mg

The median duration of exposure to alpelisib was 107.1 weeks (range: 96.3 to 120.3 weeks) and the median average daily dose received was 50.0 mg (range: 27 to 103 mg).

AEs were experienced by all 7 patients (100%), which were considered treatment related in 3 patients (42.9%). Most of the AEs were grade 1-2 in severity.

Grade ≥ 3 AEs were pneumonia (28.6%), hepatic cytolysis and haemoglobin decreased (14.3% each). SAEs were experienced by 3 patients (42.9%). The most common SAE by SOC was Infections and infestations (PT: Pneumonia), which occurred in 2 patients (28.6%), one of which was a grade ≥ 3 event. All grade AESIs reported in more than one patient were GI toxicities (nausea, diarrhoea, vomiting), experienced by 5 patients (71.4%), Stomatitis and Hypersensitivity, experienced by 2 patients (28.6%), each. There was no grade 3 AESI in Group 4. There were no AEs leading to treatment discontinuation. AEs leading to dose interruption were experienced by 3 patients (42.9%). No patients had a dose reduction due to AEs.

Other safety data

Death

No deaths were reported in patients treated with alpelisib in EPIK-P1, EPIK-P3 and EPIK-P2 studies. One death was reported in EPIK-P2 in a pediatric patient receiving placebo (Group 2) deemed to be unrelated to study treatment. This patient, died on Day 5 due to massive embolisms in multiple locations and hemolytic streptococcal group A infection.

No particular concern emerged from overdose, drug abuse and withdrawal and rebound.

Safety related to drug-drug interactions:

No dedicated drug-drug interactions studies were performed. The DDI profile of alpelisib has been adequately assessed as part of the MAA for the oncologic indications and in the post-marketing variations that followed. However, since alpelisib is a teratogen agent, the absence of a dedicated clinical interaction study with contraceptives warranted a warning in section 4.6 of the SmPC for lack of data, and a recommendation for women using systemic contraceptive steroids to add a barrier method (sections 4.4,4.5 and 4.6 of the SmPC and related sections in the PL).

Safety in special population:

Sub-group analysis for the impact of gender, race and region on safety profile based on current EPIK-P1 data were not conducted due to the small number of patients in these categories. Sub-groups for the effect of age, race and gender on safety profile were performed based on patients with breast cancer in SOLAR-1.

Besides, it is important to highlight the risk of osteonecrosis of jaw (ONJ) which was reported in cancer patients during combination with bisphosphonates or RANK-ligand inhibitors. This risk of ONJ should be considered as a matter of concern, taking into account:

- the 45 cases of osteonecrosis of the Jaw (ONJ) reported in the last PSUR for alpelisib (Piqray) indicated in oncology (Data Lock Point 23-MAY-2025);

- the uncertainties highlighted on the effects of alpelisib on bone growth and development in paediatric patients, based on non-clinical data (see also assessment of OC 96) and reported as missing information in the list of safety concerns of the RMP;

- the increased risk of early exposure to oral bisphosphonates in case of bone disorders (osteoporosis) in alpelisib treated patients, with the risk of medication related ONJ (MRONJ) development of 0.02–0.05% according to Brzak et al. (2023).

Although this risk is less than in oncology fields (cancer patients who are treated with zoledronate have a cumulative risk of MRONJ lower than 5%), it cannot be ignored for PROS patients. Hence, even though no event of osteonecrosis of jaw occurred during clinical studies, such a potential risk in this population cannot be disregarded. Therefore, based on the available data on ONJ development with alpelisib in oncology setting, and considering the uncertainties about the long-term safety, notably bone growth and development with alpelisib in PROS patients, the available data are sufficiently relevant for includig ONJ as an important potential risk in the RMP of alpelisib in PROS indication.

5.4.10.1.2. Additional safety data

The Applicant provided during the procedure updated safety data from studies EPIK-P2 and EPIK-P3 (DCO: 18 Feb 2025) as well as SAEs reported in EPIK-P2 from 25 Feb 2025 to 30 Sep 2025.

EPIK-P2

Data discussed below are based on Group 2 (All paediatrics; n=82) and 4 (n=7), since adult patients in Cohort 1 received a different dose than the one intended to be used in clinical practice.

Overall, safety results in Group 2 were consistent with the previous analysis. The most common AEs, (≥20%) were headache, pyrexia (30% each), abdominal pain (28%), diarrhoea (27%), vomiting, pain in extremity and nasopharyngitis (22%, each). Grade≥3 was reported in 28 (34.1%) patients; one additional patient from the previous DCO.

No AEs with fatal outcome were reported. SAEs were reported in 16 patients (19.5%), being 6 considered treatment-related. Only one additional SAE was reported from the previous DCO.

AEs leading to treatment discontinuation occurred in 3 patients, one additional patient from the previous DCO due to alopecia. Dose adjustments/interruptions were required in 30.5% of patients; 4 additional patients from the last DCO.

Regarding Group 4 all patients reported at least one AE, of which 3 patients reported Grade≥3 and 3 patients reported SAEs. One of these SAEs, an event of hepatic cytolysis, was considered related by the investigator. The event was resolved after alpelisib interruption. No fatal AEs or AEs leading to discontinuation were reported. Dose interruptions were required in 3 patients.

With regards to SAEs, after the 25 Feb 2025 analysis, 10 SAEs were reported in 6 patients in Groups 2 and 4, half of them considered related to the underlying disease. None of these cases required treatment discontinuation and all cases recovered. Events reported included: cellulitis (2), enterocolitis infectious (1), stomatitis (1), compression of brain (1), skin infection (1), pneumonia (1), pyelonephritis (1), inflammation (1) and pain in the leg (1).

In Group 1 (adult patients) 5 new SAEs were reported in 4 adult patients, none of them reported in more than 1 patient: epileptic seizure, drug withdrawal syndrome, acute pyelonephritis, hyperglycaemia and sepsis.

EPIK-P3

Updated data are based on a median duration of exposure of 83 months (around 7 years) since the initiation of treatment in the compassionate use program (3-year prospective data).

During this period, an increase in the incidence of AEs is observed, mainly in the sub-group of paediatric patients, although most of AEs were Grade 1 or 2 with only 3 additional Grade≥3 AEs (1 paediatric patient and 2 adult patients). The overall incidence of AEs was 62.5%, AEs Grade≥ 3 22.5%. SAEs were reported in 7 (17.5%) patients, 2 additional patients from the previous DCO. No fatal AEs or AEs leading to discontinuation were reported. The number of patients that required dose reductions/interruption was low.

5.4.10.2. Conclusions on clinical safety

The safety data of alpelisib administered as monotherapy for the treatment of adult and paediatric patients aged 2 years and older with PIK3CA-related overgrowth spectrum (PROS), is based on the population who received, at least, one dose of alpelisib at the intended dose across 3 clinical studies: EPIK-P1 (pivotal study), EPIK-P3 (retrospective period and 1-year prospective period) and the supportive study EPIK-P2, in 146 patients (18 adult and 128 paediatric patients). Overall, the safety profile observed in patients with PROS is consistent with the mechanism of action of alpelisib and comparable to the known safety profile of alpelisib (already authorised in breast cancer).

Most patients experienced at least one adverse event, and most of them were mild to moderate in severity. The main AEs are characterized by gastro-intestinal toxicity (e.g. nausea, vomiting, diarrhoea and aphthous ulcer), metabolism and nutrition disorders (e.g. hyperglycaemia), skin and subcutaneous disorders (e.g. dry skin, acne, alopecia) and clinical chemistry abnormalities (e.g. blood phosphorus decreased, blood calcium decreased, blood creatinine increased).

Across both EPIK-P3 and EPIK-P2, a lower rate and severity of treatment-related grade ≥ 3 AEs and AESIs was observed in paediatric patients (< 18 years) compared to adult patients (≥ 18 years). This suggests that a higher alpelisib exposure can be associated with a slightly higher incidence of AEs (i.e, rash, alopecia, hyperglicaemia, GI toxicity). Moreover, there are differences in effect between each paediatric age group versus the adult group on AE risk.

The AESIs selected for alpelisib were GI toxicity (nausea, vomiting, and diarrhoea), hyperglycaemia, alopecia, hypersensitivity, severe cutaneous reactions, rash, stomatitis, pneumonitis, and pancreatitis. These AESIs may be associated with the use of alpelisib and can, in general, be effectively managed with appropriate concomitant medications, or alpelisib dose interruption and/or modification.

Even though no adverse events of pneumonitis and severe cutaneous adverse reactions were observed in PROS patients, a warning was deemed necessary and is stated in the SmPC, and both are considered as important potential risks in the safety concerns of the RMP and are expected to be addressed through appropriate additional PV activities (2 ongoing category 3 studies).

The main uncertainty is the long-term safety profile of alpelisib notably its impact on growth and development. Treatment duration is still insufficient to characterise the long-term effect of alpelisib in PROS patients, particularly regarding the potential impact on growth, development and puberty in paediatric patients with PROS. This risk is considered as missing information in the RMP and is expected to be addressed through appropriate additional PV activities (the 2 ongoing category 3 studies).

In conclusion, alpelisib safety profil appear to be in line with the known safety profil in the oncology setting and is manageable through routine risk minimisation measures and clinical management. The safety data generated in the PROS indication is limited however it is considered acceptable in view of the rarity of the disease. Uncertainties related to safety risks are expected to be addressed through adequate additional pharmaciviglance activities (2 ongoing category 3 studies and the SOB imposed in the framework of the conditional MA).

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 52: Summary of safety concerns in the RMP

Important identified risks	Hyperglycaemia
Important potential risks	Severe cutaneous adverse reactions Pneumonitis Reproductive toxicity, including impaired fertility Osteonecrosis of the jaw
Missing information	Safety with long-term use, including effects on growth, development and puberty

The proposed list of safety concerns is considered acceptable and adequate in view of the safety discussion and conclusions detailed above.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

Routine pharmacovigilance activities

An event specific follow-up checklist will be used to collect further data to help characterize and closely monitor the important identified risk 'Hyperglycemia (Life threatening and fatal) and Complications of Hyperglycemia (serious cases only).

Additional pharmacovigilance activities

Table 23: Planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
CBYL719F12201 (EPIK-P2): A Phase II double-blind study with an upfront, 16- week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS). Ongoing	This study will assess the efficacy, safety and pharmacokinetics of alpelisib in participants of different ages with confirmed diagnosis of PROS.	Hyperglycaemia, severe cutaneous adverse reactions (SCARs), Pneumonitis, Osteonecrosis of the jaw, Safety with long term use, including effects on growth development and puberty	Interim report submission with PSUR Final clinical study report submission	31-Oct-2028 31-Dec-2031
CBYL719F12401 (EPIK-P3): A phase II study to evaluate the longterm safety and efficacy of alpelisib in patients with PIK3CA-Related Overgrowth Spectrum (PROS) who previously participated in Study CBYL719F12002 (EPIK-P1). Ongoing	This study will assess the long-term safety and efficacy of alpelisib treatment in pediatric and adult participants with severe or life-threatening complication of PROS who participated in EPIK-P1 and continued to receive treatment with alpelisib after the EPIK-P1 cut-off date in the context of the global compassionate use program.	Hyperglycaemia, severe cutaneous adverse reactions (SCARs), Pneumonitis, Osteonecrosis of the jaw, Safety with long term use, including effects on growth and development	Final clinical study report submission	30-Sep-2028

Plans for post-authorisation efficacy studies

Table 24: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of Objectives	Efficacy uncertainties	Milestones	Due Date

		addressed		
EPIK-P4: A Phase II single arm study to assess the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CArelated overgrowth spectrum (PROS) BYL719F12202 Planned	This study will demonstrate the efficacy of alpelisib (proportion of participants with a confirmed objective response by BIRC) in at least one of Group 1 (Adult patients) or 2 (pediatric patients: 2 to <18 years of age)	Long-term efficacy and safety Assess the efficacy and safety of higher starting doses in adult and pediatric patients ≥6 years of age	Final report submission	31-Dec-2032

EPIK-P4 is imposed as a specific obligation in the context of the conditional MA for Vijoice. Further details about the study are provided in section 9.6.3.3.

6.3. Risk minimisation measures

6.3.1.1. Routine risk minimisation measures

The routine risk minimisation measures for Vijoice are summarised in table 25.

Table 25: Planned routine risk minimisation measures

Safety concern	**Routine risk minimisation activities**
Hyperglycaemia	Routine risk communication: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Vijoice PL Section 4 Possible side effects
Severe cutaneous adverse reactions	Routine risk communication: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use PL Section 2 What you need to know before you take Vijoice (Warnings and precautions)
Pneumonitis	Routine risk communication: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use PL Section 2 What you need to know before you take Vijoice (Warnings and precautions) Other routine risk minimization measures beyond the Product Information: None
Reproductive toxicity, including impaired fertility	Routine risk communication: SmPC section 4.4 Special warnings and precautions for use SmPC section 4.6 Fertility, pregnancy and lactation SmPC Section 5.3 Preclinical safety data PL Section 2 What you need to know before you take Vijoice (Pregnancy and breastfeeding)

Osteonecrosis of the jaw	Routine risk minimization activities: None.
Safety with long-term use, including effects on growth and development	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use PL Section 2 What you need to know before you take VijoiceRoutine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None

The routine risk minimization activities as described above are considered sufficient to manage the safety concerns related to Vijoice.

6.3.1.2. Additional risk minimisation measures

No additional risk minimisation measures are deemed necessary, and it is considered that the routine risk minimization measures are sufficient to mitigate the safety risks related to the use of alpelisib in the PROS indication.

6.4. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 2.3 dated 21-May-2026 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

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

7.2. Periodic safety update reports (PSURs) submission requirements

Based on the different target populations for different indications for alpelisib, the PRAC rapporteur is of the opinion that a separate entry in the list of Union reference dates (EURD list) for Vijoice is needed, as it cannot follow the already existing entry for alpelisib.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the European birth date (EBD) to determine the forthcoming Data Lock Points.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical study, EPIK-P1, which evaluated alpelisib in patients aged 2 years and older with severe or life-threatening manifestations of PIK3CA-related overgrowth spectrum (PROS). No additional restrictions with respect to age, weight, or other patient-related factors were considered necessary.

8.1.2. SmPC section 5.1 justification

Information related to EPIK-P1 as pivotal study for this application and to EPIK-P3 providing supportive data is included in the SmPC section 5.1.

8.2. Labelling

8.2.1. User consultation

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

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vijoice (alpelisib) is included in the additional monitoring list since it is approved under a conditional marketing authorisation [REG Art 14-a].

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

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Vijoice (alpelisib) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor.

The indication applied for is:

"Vijoice is indicated 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."

PIK3CA-related overgrowth spectrum (PROS) is a group of rare syndromes caused by somatic mutations in the PIK3CA gene. These mutations occur during embryogenesis, and the clinical presentation varies depending on timing and tissue affected. PROS typically manifests as congenital or early-onset, segmental, and progressive tissue overgrowth. The overgrowth is sporadic and exhibits a mosaic distribution pattern. Affected individuals may show abnormalities in cutaneous, vascular, musculoskeletal, or cerebral systems.

Overgrowth can be focal or segmental and may persist or worsen into adulthood. Severity ranges from mild localized overgrowth to extensive, life-threatening involvement of major organs or vessels. Vasculature and adipose tissue are commonly and prominently affected. Other tissues such as bone, brain, nerves, liver, and muscle may also be involved. Clinical complications vary and can include pain, seizures, developmental delays, thrombosis, and organ dysfunction. These complications can lead to significant disability and, in some cases, early mortality, especially in children. PROS encompasses a broad spectrum of phenotypes with overlapping features. Recognized syndromes include FAO, HHML, CLOVES, MCAP, CLAPO, and KTS, among others.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1 of this document.

There is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for this disease. Current treatment relies on supportive care and is comprised of surgical debulking, amputations, orthopaedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure). Patients often experience recurrence following surgery, and repeated surgeries are frequently required. Therefore, patients with severe or life-threatening manifestations of PROS have a significant unmet medical need for new and effective pharmacological treatments that target the underlying cause of the disease (i.e. PIK3CA mutation) which is currently unavailable.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3 of this document.

The main evidence of efficacy submitted are based on 3 clinical studies.

EPIK-P1: a retrospective chart review of patients of 2 years of age and older with severe or life-threatening PROS who have received alpelisib for at least 24 weeks as part of a compassionate use program at select sites. This study abstracted data from all eligible patients (n=58) at all participating sites that had been previously recorded in the medical charts to assess the efficacy and safety of alpelisib for the treatment of the manifestations of PROS.

A total of 57 subjects were included across 7 sites, most of them from France, Ireland and Spain. 52 out of 57 subjects continued on treatment as of the DCO of 9 March 2020. Of the 57 subjects included, 37

had at least one target lesion selected by imaging at the index date (by ICRR) and 32 out of 37 had an imaging assessment at 24 weeks. These 32 subjects constitute the complete case population for the assessment of the primary endpoint.

The primary endpoint was the response (yes/no) at Week 24 or 6 months (± 4 weeks), defined by achieving a ≥ 20% reduction from index date in the sum of measurable target lesion volume (1 to 3 lesions, via ICRR of imaging scans), provided that none of the individual target lesions have ≥ 20% increase from the index date and in the absence of progression of non-target lesions and without new lesions. Secondary endpoints were notably changes in the sum of all measurable (target and/or non-target) lesion volume over time, duration of response, and changes in signs/symptoms, concomitant medication and functional status.

EPIK-P3: an ongoing multicentre, interventional, open-label study in paediatric and adult patients with severe or life-threatening complications of PROS who participated in EPIK-P1, and who continued to receive treatment with alpelisib after the EPIK-P1 cut-off date. An initial retrospective (non-interventional) period, started on 10-Mar-2020 (one day after the EPIK-P1 data cut-off date), included 48 patients. A subsequent prospective (interventional) period, started on the day of the first interventional dose administration in the prospective period of each respective patient included 40 patients. The patients have data collected for approximately 3 years in the retrospective period and will be followed up for at least 5 years in the prospective period.

The primary objective of the study is to assess the long-term safety and tolerability of alpelisib based on the frequency of severe AEs (CTCAE Grade ≥ 3) over time. Overall clinical response was assessed by the investigators based on clinical judgement and pre-defined criteria which included a combination of clinical evaluation of the patient's general conditions and radiological imaging. The overall clinical response was noted as improved, stable, or worsened, as compared to the previous assessment performed.

EPIK-P2: an ongoing prospective multi-centre trial with an initial 16-week, randomized, double-blind, placebo-controlled period, followed by two extension periods (24 to 48 weeks and 48 weeks-5 years) in paediatric and adult patients with symptomatic and/or progressive overgrowth and at least one measurable lesion as confirmed by BRIC.

The primary endpoint was the confirmed responder rate after all patients had reached week 48 or discontinued as defined by an at least 20% volume decrease of a sum of 1 to 3 target lesions volume provided that none of the target lesions has progressed by ⩾ 20% from baseline and in the absence of progression of non-target lesions and new lesions in patients initially randomized in the alpelisib arm by BIRC (blinded independent review committee).

The most relevant group of patients for the primary analysis is the paediatric population aged 6-17 years (starting dose 50 mg) as the starting dose for adult patients in this study (125 mg once a day with food) does not correspond to that claimed in the label (250 mg once a day with food) and the 3 other paediatric groups are only exploratory.

9.3. Favourable effects

EPIK-P1

The proportion of patients with response at Week 24 (± 4 weeks) in the complete case population was 37.5% (12/32 patients) with 95% CI: 21.1; 56.3 based on independent central radiology review. The primary endpoint of the study was met.

Supportive sensitivity analyses conducted based on the efficacy population (n=37), showed the response rate was not affected by the change in methods to deal with missing response (n=5). The resultant response rates ranged from 32.4% (worst case scenario) to 45.9% (best case scenario) and were consistent to the result of the primary analysis (37.5%).

The primary efficacy endpoint was reported for the following sub-groups: age; sex; mutation type; PROS sub-type; and lesion location.

Among the 12 patients with a response at Week 24 (7 paediatric patients and 5 adult patients), the median DOR was not estimable as no event (progression or death) was reported at the time of the data cut-off date. The median time to censoring was 63.3 weeks, corresponding to approximately 14.6 months (range: one day to 186.7 weeks)

Among the 31 patients who had an imaging assessment at the index date and at Week 24, the mean percentage change, in the sum of target lesion volume (1 to 3 lesions), as assessed by ICRR was -13.7% (range: -57.1% to 15.0%).

Treatment with alpelisib was associated with reduction in the use of concomitant medications to manage PROS (index date: 34/57 patients, 59.6%; Week 24: 30/56, 53.6%; end of study 25/57 patients, 43.9%) in the full population.

At Week 24, an improvement was reported in the 5 most reported PROS-related signs and symptoms (fatigue, vascular malformation, limb asymmetry, disseminated intravascular coagulation, and pain) in a majority of patients. The improvement was consistent across age groups in the full population.

EPIK-P3

Of the 52 patients who terminated EPIK-P1, 48 patients were enrolled in EPIK-P3 and none discontinued treatment during the retrospective period. Of the 48 patients who terminated the retrospective period, 40 patients (31 paediatric and 9 adults) were enrolled in the prospective period.

The EPIK-P3 results showed that most patients had improved (9/40 [22.5%]) or stable (29/40 [72.5%]), Overall lesion response during the first 12 months of the prospective period compared to the previous assessment and stabilisation in most representative PROS-related signs and symptoms sustained with long-term treatment. The EPIK-P3 data would support the benefit of alpelisib treatment in the long term, with a benefit demonstrated and attributed to the treatment with alpelisib.

The proportion of patients in the efficacy population with a confirmed response at any time during the 3-year period was 15/37 (40.5%) (95% CI: 24.8%, 57.9%) as assessed by BIRC.

EPIK P2

The proportion of patients with confirmed response after all patients reached week 48 or discontinued was 23.2% (13/56) in the paediatric population even if the primary objective was not met.

At the end of the placebo-controlled period (week 16), the proportions of patients with response in the alpelisib arm were 11.1% (6/54) in the adult group and 8.9% (5/56) in the paediatric group versus no responses in the placebo arms.

With update from an interim analysis with a later cut-off (18-Feb-2025), 3 new confirmed responses were achieved after dose escalation in the alpelisib arm (response rate of 28.6%, (97.5% CI: 16%-44.1%)) and 2 new confirmed in the placebo arm after switching to alpelisib were observed in the paediatric group.

Overall, clinical response showed either clinical improvement or stability in the majority of patients at week 16 and an increased proportion of patients demonstrated clinical improvement at Week 48.

9.3.1. Uncertainties and limitations about favourable effects

The current MAA is largely based on retrospective data, mainly from the pivotal retrospective study EPIK-P1, with 57 patients treated, with primary efficacy outcome results available for 32 patients (complete case population). EPIK-P1 is an open-label, non-controlled study, with small sample size and data being retrieved from a retrospective chart review, and lack of an internal comparator.

Data from EPIK-P3 would support the the durabilty of alpelisib treatment in the long term, with a benefit demonstrated in the intended indication. However, in EPIK-P3 there was a lack of standardisation in the follow-up and patients' evaluation for efficacy.

The overall efficacy data package is rather limited, it includes 57 patients treated in the EPIK-P1 (only 32 comprised the population for the primary analysis), 40 of which continued onto the EPIK-P3. Data from the ongoing EPIK-P2 study (81 adults +84 paediatric patients) are considered results should be interpreted with caution given that the 40 patients included represent the most favourable selected subset of the 58 patients of EPIK-P1, i.e. those who perceived benefit from treatment. In addition, there was a lack of standardisation in the follow-up and patients' evaluation for efficacy.

The EPIK-P2 study is the only controlled study conducted with alpelisib in the treatment of PROS, and included a broader population than the target population and used a different dosing regimen than the one intended for the registration (and in EPIK-P1) and did not meet its primary efficacy endpoint. In addition, the duration of the placebo-controlled period (16 weeks) was too short to observe any meaningful differences. Therefore, these data are considered supportive and cannot be considered as confirmation and/or replication of the results from EPIK-P1.

The PROS population is heterogeneous by default in terms of phenotypes and types of lesions. In addition, there is not a universally accepted definition for disease severity. These issues question the external validity of the results. It was however clarified, notably by the clinical experts that tumour reduction observed in patients with PROS are most likely attributable to alpelisib (in view of te natural history of the disease and the absence of other treatment administered). Also experts considered that the proposed criteria in the applicant's algorithm are valid to define severity of PROS manifestations.

No specific dose-response studies have been performed with alpelisib for the treatment of PROS. Although a different starting dose for adults was attempted in EPIK-P2, the dose currently proposed for marketing in both adults (250mg QD, taken with food) and paediatric patients (50mg QD) are based on those used in the original compassionate use programme, with some modifications regarding the possibility to escalate dose in paediatric patients for treatment optimization after 6 months on the starting dose and the intake with food. Overall, there are still uncertainties on whether the proposed posology in the paediatric population is adequate given the low rates of responses observed in the paediatric population and the rate of dose increase in EPIK-P2. This uncertainty will be addressed as part of the specific obligation imposed in the context of the conditional MA.

9.4. Unfavourable effects

The overall safety data of alpelisib in PROS patients are consistent with its mechanism of action and its known safety profile in the breast cancer indication. Most patients experienced at least one adverse event, and most of them were mild to moderate in severity.

From the pooled EPIK-P1/EPIK-P3 safety dataset, almost half of patients experienced serious AEs (42.1%; 30.8% in paediatric patients and 66.7% in adult patients) but most of them may be attributed to the underlying or concurrent conditions of PROS. The main preferred terms were lipoma (all patients 5.3%), cellulitis (all patients 3.5%), dehydration (all patients 3.5%) and pain in extremity (all patients 3.5%). One treatment-related SAE reported in alpelisib arm was infection.

In the EPIK-P2 study group 2, during the placebo-controlled period, the incidence of SAEs in paediatric patients was 5.4% in the alpelisib arm and 7.1% in the placebo arm. SAEs that were reported in the alpelisib arm included asthma, COVID-19 and infection.

During the alpelisib period, the incidence of individual SAEs was 18.3% and 11% had Grade ≥ 3 SAEs. The most frequent reported SAE was cellulitis and growth retardation. SAEs assessed as suspected to be study treatment related by the investigators were reported in 7.3% of patients, and Grade ≥ 3 SAEs in 6.1% patients. The most frequent SAE considered to be related to study treatment was growth retardation in three patients, although in most cases it seems that this is not impacting the overall grow development.

The main adverse reactions are characterized by gastro-intestinal toxicity (e.g. nausea, vomiting, diarrhoea and aphthous ulcer), metabolism and nutrition disorders (e.g. hyperglycaemia), skin and subcutaneous disorders (e.g. dry skin, acne, alopecia) and clinical chemistry abnormalities (e.g. blood phosphorus decreased, blood calcium decreased, blood creatinine increased). Most of adverse reactions appear manageable in the clinical setting.

Even though no adverse event of special interest (AESI) of pneumonitis and sever cutaneous adverse reactions were observed during EPIK-P1, EPIK-P3 and EPIK-P2 group 2 studies in PROS patients, a warning is included in section 4.4 of the SmPC and these risks are listed in the RMP as important potential risks and are expected to be addressed through appropriate additional PV activities (2 ongoing category 3 studies).

9.4.1. Uncertainties and limitations about unfavourable effects

The safety profile of alpelisib in the currently proposed PROS indication is mainly based on retrospective data. Further the safety database is limited. A limited number of patients have been exposed to alpelisib treatment for PROS at the proposed dosing regimen, particularly adult patients. Besides, the number of patients aged between 2–5 years is small, and uncertainty remains regarding the safety profile in this sub-group. This is however acceptable in view of the rarity of the disease.

Moreover, treatment duration is still considered insufficient to characterise the long-term effect of alpelisib in PROS patients, even more considering the potential impact of alpelisib on growth, development and puberty in paediatric patients with PROS. AEs of growth retardation have been observed in patients treated with alpelisib, although in most cases it seems that this is not impacting the overall growth development. Nevertheless, while it is not possible to unequivocally conclude on a causal relationship between alpelisib and grow development delay, due to the limitations of the safety data set, a deleterious impact cannot be ruled out either. This risk is considered as missing information in the RMP

and is expected to be addressed through appropriate additional PV activities (the 2 ongoing category 3 studies).

Besides, adverse events of osteonecrosis of jaw (ONJ) were reported with alpelisib in the oncology setting in combination with bisphosphonates or RANK-ligand inhibitors, and it is currently mentioned in the Piqray SmPC. Therefore, even though no event of ONJ occurred during clinical studies for the PROS indication, such a potential risk in this population cannot be disregarded and it is therefore included as an important potential risk in the RMP and is expected to be further investigated and addressed through appropriate additional PV activities (the 2 ongoing category 3 studies).

Consequently, there are still some uncertainties and limitations to characterise the actual safety profile of alpelisib in patients with PROS. These are expected to be addressed through the appropriate additional pharmacovigilanve activities agreed for Vijoice in the RMP and the specific obligation imposed as part of the CMA.

9.5. Effects table

Table 53: Effects Table for Vijoice in the PROS indication (Jul 2025).

Effect (short description)	*Treatment*		*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects					
Responders at Week (n/N) 24 % (95% IC)	Overall:37.5 % (21.1, 56.3) Adult: 55.6% (21.2, 86.3) Paediatric Patients: 30.4 % (13.2, 52.9)			Proportion of patient with confirmed radiologic response Unc: retrospective chart review	EPIK-P1 study
Duration of response	Overall NR (0.03+, 42.9+) – paediatric patients			Median DOR (month)	EPIK-P1 study
Responders at Week 24 % (n/N) (95% IC)	23% (13/56) (12,38)			Proportion of patient with confirmed radiologic response p < 0.1364	EPIK-P2 study Cohort 2
Response rate at Week 16 % (n/N) (97.5% IC)	9 (5/56) (12, 38)		0 (0/28) (0.0, 12.3)	Secondary endpoint	EPIK-P2 study Cohort 2
Duration of response	Paediatric patients NR (9.1+, 80.1+)			Median DOR (month)	EPIK-P2 study Cohort 2
Unfavourable effects					

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Blood phosphate decreased	Paediatric patients: 27/39 (69.2%) Adult patients: 11/18 (61.1%)		-	Repeated post-baseline decreases, mostly of mild (Grade 1) severity, were noted in several patients in EPIK-P1/EPIK-P3 safety population.	Pool EPIK-P1/EPIK-P3 retrospective period
	-		-	No ADR during EPIK-P2* (group 2: paediatric patients 6-17 y)	EPIK-P2* (group 2: paediatric patients 6-17 y)
Blood calcium decreased	Paediatric patients: 25/39 (64.1%) Adult patients: 11/18 (61.1%)		No related event in EPIK-P2 placebo controlled period**	Post-baseline decreases, mostly of mild (Grade 1) severity, were noted in several patients. Known ADR in the oncology setting.	Pool EPIK-P1/EPIK-P3 retrospective period
					EPIK-P2* (group 2: paediatric patients 6-17 y)
Blood creatinine increased	Paediatric patients: 19/39(48.7%) Adult patients: 2/18 (11.1%)		-	Repeated post-baseline decreases, mostly of mild (Grade 1) severity, were noted in several patients in EPIK-P1/EPIK-P3 safety population.	Pool EPIK-P1/EPIK-P3 retrospective period
	Paediatric patients: 4/82 (4.9%)		No related event in EPIK-P2 placebo controlled period**		EPIK-P2* (group 2: paediatric patients 6-17 y)
Glucose increased	Paediatric patients: 8/39 (20.5%) Adult patients: 4/39 (22.3%)		-	On target effect of PIK3CA inhibition	Pool EPIK-P1/EPIK-P3 retrospective period
	Paediatric patients: 1/82 (1.2%)		No related event in EPIK-P2 placebo controlled period**	On target effect of PIK3CA inhibition	EPIK-P2* (group 2: paediatric patients 6-17 y)
Lipase increased	Paediatric patients: 2/82 (2.4%)		No related event in EPIK-P2 placebo controlled	Repeated post-baseline decreases, mostly of mild (Grade 1) severity, were noted in several patients in EPIK-P1/EPIK-P3 safety population.	EPIK-P2* (group 2: paediatric patients 6-17 y)

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Diarrhoea	Paediatric patients 5/39 (12.8%) Adult patients: 5/18 (27.8%)		-	AESI. Frequently reported in PROS patients.	Pool EPIK-P1/EPIK-P3 retrospective period
	Paediatric patients: 9/82 (11%)		Paediatric patients: 1/56 (1.8%)**	AESI. Frequently reported in PROS patients.	EPIK-P2* (group 2: paediatric patients 6-17 y)
Nausea	Paediatric patients: 1/39 (2.6%) Adult patients: 2/18 (11.1%)		-	AESI. Frequently reported in PROS patients.	Pool EPIK-P1/EPIK-P3 retrospective period
	Paediatric patients: 7/82 (8.5%)		Paediatric patients: 5/56 (8.9%)**		EPIK-P2* (group 2: paediatric patients 6-17 y)
Rash	-		-		
	Paediatric patients: 4/82 (4.9%)		Paediatric patients: 2/56 (3.6%)**	AESI. Frequently reported in PROS patients.	EPIK-P2* (group 2: paediatric patients 6-17 y).
Dermatitis	Paediatric patients: 1 (2.6%) Adult patients: 3 (16.7%)			Frequently reported in PROS patients. Skin reactions (incl. rash, acne, dermatitis acneiform) are frequent with alpelisib, and some features overlap.	Pool EPIK-P1/EPIK-P3 retrospective period.
	Paediatric patients: 1/82 (1.2%)				EPIK-P2* (group 2: paediatric patients 6-17 y).

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; <sBA: serum bile acids>; <PELD: paediatric end-stage liver disease>; <MELD: model for end-stage liver disease score>; <SBD: surgical biliary diversion>; <OLT: orthotopic liver transplantation>; <PE: primary endpoint>; <SE: secondary endpoint>; <OR: odds ratio>.

*** EPIK-P2 group 2** safety data refers to the alpelisib-treatment period which includes paediatric patients who received at least one dose of alpelisib, including patients who switched from placebo to alpelisib after the 16-week placebo-controlled period. Source: EPIK P 2cbyl719f12201sep2024--report-body Table 14.3.1-1.11;

**** EPIK-P2 group 2** placebo-controlled period CSR preliminary analysis placebo-controlled period table 14.3.1-1.12.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The indication applied for in the application for Vijoice is 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.

There is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for this disease. Current treatment relies on supportive care and is comprised of surgical debulking, amputations, orthopaedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure). Patients often experience recurrence following surgery, and repeated surgeries are frequently required.

There is a robust mechanistic rationale for the use of alpelisib in the treatment of PROS. The mutations in the PIK3CA gene lead to hyperactivation of the PI3K/AKT/mTOR pathway and to the development of heterogeneous mosaic segmental overgrowth disorders (PROS). Alpelisib is an α-specific PI3K inhibitor which has demonstrated clinical benefit in solid tumours (notably breast cancer), as well as activity in both in vitro and in vivo non-clinical models of PROS. Available data, including the ICRR review suggest that the tumour reduction observed in some patients with PROS are attributable to treatment with alpelisib.

For this application, the pivotal evidence to support the clinical efficacy of alpelisib in patients with PROS is based on radiologic responses from a retrospective chart review of 32 adults and paediatric subjects treated under the compassionate use programs (EPIK-P1), data from an open label study in subjects previously treated in EPIK-P1 (EPIK-P3) and supportive data from a placebo controlled study (EPIK-P2).

The decrease of tumour volume seen in the clinical studies is considered attributed to alpelisib. The exact effect size of alpelisib treatment on volume/growth rate remains unknown however:

- radiologic responses based on an independent central radiology review showed a reduction of target tumour size.
- a positive improvement was observed in the 5 reported PROS-related signs and symptoms (fatigue, vascular malformation, limb asymmetry, disseminated intravascular coagulation, and pain) in a majority of patients
- it is plausible that a decrease in tumour volume is associated with a decrease in the PROS symptoms

CHMP also considered views from clinical experts within an AHEG. The AHEG confirmed that spontaneous regression of PROS is unlikely, with lesion enlargement expected to occur in the absence of treatment. As no concomitant therapies were administered during the clinical studies, the observed effect is most likely attributed to alpelisib. Experts also indicated that while a 20% volume reduction shows clinical effect, given the disease's heterogeneity, its clinical significance in PROS depends on lesion location and symptoms and even minor volumetric changes (e.g., in neck lesions) could be impactful for patients. They also noted that clinical benefits (e.g., pain relief, improved functionality, or quality of life) could occur without radiological changes.

Methodological limitations are raised for the pivotal study (EPIK-P1), including the open-label, non-controlled design, data being retrieved from a retrospective chart review, a lack of an internal comparator and the small sample size. The open label design and the sample size could be understood in view of the rarity and the severity of the condition.

The supportive data also raise methodological issues: in EPIK-P3 there was a lack of standardisation in the follow-up and patients' evaluation for efficacy and EPIK P2, the only controlled study conducted with alpelisib in the treatment of PROS, included a broader population than the target population and used a different dosing regimen than the one intended for the approval and did not meet its primary efficacy endpoint.

With regards to the safety, the overall safety data of alpelisib in PROS patients are consistent with its mechanism of action and its safety profile in breast cancer indication. The majority of patients experienced at least one adverse event, and most of them were mild to moderate in severity. Most of adverse reactions are manageable in the clinical setting and through routine risk minimisation measure. No additional risk minimisation measures are deemed neccesary. The main uncertainty is the long-term safety profile of alpelisib notably its impact on growth, development and puberty. This uncertainty is considered as missing information in the RMP and is expected to be addressed through appropriate additional PV activities (the 2 ongoing category 3 studies).

Taking into account the above and in view of the rarity of the disease, the severity of the indication applied for and the unmet medical need in patients with PROS, the benefit-risk profile of Vijoice is considered positive. In view of the uncertainties described above, the available data are considered not comprehensive. Therefore, a conditional marketing authorisation is appropriate.

In the context of the CMA, the applicant will conduct as a specific obligation, a Phase II single arm open-label, multi-center study to confirm the efficacy, safety and pharmacokinetics of alpelisib in paediatric and adult patients with PROS (EPIK-P4). This study will include a minimum number of severe or life-threatening participants. The single-arm trial design is considered acceptable considering the severe population and the ethical aspects as raised by the AHEG.

9.6.2. Balance of benefits and risks

Based on the available efficacy data and the acceptable safety profile in the PROS setting, the benefit-risk of Vijoice is considered positive in the proposed indication for a conditional approval.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Early Dialogue with CHMP

In the framework of the CHMP early dialogue, input from patients was provided. Details are included in section 5.3.6 of this report.

9.6.3.2. Input from additional experts

Upon request from the CHMP, an Ad hoc expert group meeting (AHEG) was convened on 13 March 2026, in the context of an ongoing initial marketing authorisation procedure.

The below summarises the CHMP question to the AHG and their responses.

1. Considering the natural history of PROS and the heterogenicity of the different phenotypes, please discuss whether the observed responses could be unequivocally attributed to treatment with alpelisib.

The experts largely agreed that no spontaneous regression in PROS is expected. In the absence of any intervention, the lesion will most likely get bigger and the question is rather how fast it would progress.

Therefore, the experts are of the view that the effect observed in the studies is most likely attributed to alpelisib, in particular as no other treatment was administered.

One of the experts raised the case of lymphatic malformations which are part of the PROS and where a change of volume of the lesions might occur with or without treatment (e.g due to infection) and would not therefore be necessarily attributed to treatment.

The heterogeneity of the disease was highlighted with, as a consequence, the heterogeneous results observed. The rarity of the disease was also noted.

2. In the event that the responses could be solidly attributed to alpelisib treatment, please discuss whether the observed radiologic responses are likely to translate into clinical benefit for PROS patients.

The majority of the experts confirmed that the radiological image is the most objective tool to measure the reduction of the lesions.
Experts highlighted that the reduction of the lesions' volume would lead to clinical improvement but the magnitude of reduction needed depends on lesion type and symptoms. They however indicated that a clinical improvement could also be observed in patients without reduction of the lesions' volume and therefore without an impact on the radiological measurement.
One of the experts noted the difficulty for some radiologists to quantify accurately the volume of lesions.

Therefore, whilst the radiological measurement is the most objective way to measure the response to treatment, other parameters (e.g pain, coagulopathy, functionality, quality of life, growing-child aspects) should also be considered for these patients.

The experts referred to a preference for a flexible approach that could be adapted to the patients' medical needs e.g the use of scales such as the OVAMA scale which is designed for patients with vascular anomalies and also available in different languages. The CTCAE was also mentioned with the 5 grades attributed depending on the symptoms of the patients. It was also highlighted that questionnaires related to quality of life are important in considering the effect of the treatment. Other questionnaires, such as PedsQL, were also mentioned.

The experts also discussed the endpoint of 20% reduction of the lesions' volume. They highlighted that a 20% reduction in lesion volume can represent a meaningful improvement but they also emphasised that in PROS, the clinical relevance of change depends strongly on lesion location and clinical symptoms. Given the variability of the PROS and the wide range of lesion presentations, even a minimal change of volume could be significant for patients, depending on the location of the lesions and the consequent clinical symptoms (e.g reduction of lesions in the neck).
Some patients have had significant improvement of their symptoms without meeting the 20% of lesions reduction (e.g improvement in breathing, improvement of mobility...). For these cases the treatment is considered beneficial.

With regards to the response rate in EPIK-P1 (37,5%), the experts considered the 37% radiological response rate from the study relevant but emphasised that radiology alone does not capture the full clinical picture and indicated again that the radiologic response is not the only parameter to quantify the response to treatment in PROS patients. They highlighted that non-responders in the study may still benefit clinically. Clinical improvement could be observed in some patients without necessarily translating into the set volume reduction of 20% and the consequent radiological response.

The experts also agreed that some patients might not respond to the treatment considering the heterogeneity of the disease.

3. Would the Applicant's algorithm be an adequate tool to identify a severe PROS population? Please discuss/justify.

The experts considered that the algorithm proposed by the company to classify the severity of the disease is valid with some comments. They commented not to include i) the treatment with opioids at baseline and ii) the requirement for a prior surgery, to classify severe cases.
The experts also stated that quality of life criteria should be considered in this algorithm.

Experts noted for some grade 2 cases, surgery might not be suitable and therefore the patients could benefit from alpelisib. The same applies to paediatric patients where it is expected that the lesions would evolve with time, and it would be beneficial to introduce a treatment as soon as possible. However further data related to long-term safety would be expected before extending the treatment to this non-severe population, in particular in children.

In conclusion, it was agreed that the proposed criteria in the Applicant's algorithm are valid to define severity except for the treatment with opioids at baseline and the requirement for a prior surgery; the inclusion of quality of life questionnaire was considered relevant to be incorporated.

4. In light of the limited data available on the performance of alpelisib for the treatment of PROS, the experts are invited to discuss:

a) whether Study EPIK-P4, is adequately designed to provide confirmatory data on the efficacy and safety of alpelisib in the target condition.

b) Given the large number of patients included in the MAP, would it be feasible to conduct a randomized, placebo-controlled trial once alpelisib is commercially available? If so, how might this study be designed (inclusion criteria, comparator, endpoints etc).

a) The experts noted improvements from earlier studies and noted that EPIK-P4 included several secondary endpoints beyond the radiological endpoint. However in EPIK-P4, the fixed dosing (not correlated with weight) is considered sub-optimal for the paediatric population. Also the granules are sub-optimal for use with nasograstic tubes.

With regards to the study design, as the data is expected to be generated for severe patients in the framework of this marketing authorisation application, the single arm design is considered acceptable. It would be rather difficult to have a placebo-controlled trial for the severe PROS patients. Experts agreed that single arm trial could still provide robust confirmation of the benefit in this severe population.
A proposal to improve EPIK-P4 could be to include the severity score and quality of life questionnaire mentioned above.
The experts referred to some ongoing placebo-controlled phase 2 trials; however, these are small in size compared to the EPIK-P4. In addition, alpelisib is not currently widely available.

b) With regards to conduction of a randomized, placebo-controlled trial once alpelisib is available on the EU market, the experts are of the view that this would be feasible and justifiable for non-severe patients. For patients with severe PROS, the use of placebo-controlled trial would not be considered ethical for the experts.
The experts emphasised the aspect of long-term safety assessment of alpelisib especially in children.
Other aspects highlighted: using the study to validate the proposed severity scores, including patients with progression risk rather than only the severe group.

9.6.3.3. Conditional marketing authorisation

9.6.3.3.1. Applicant's request for Conditional marketing authorisation

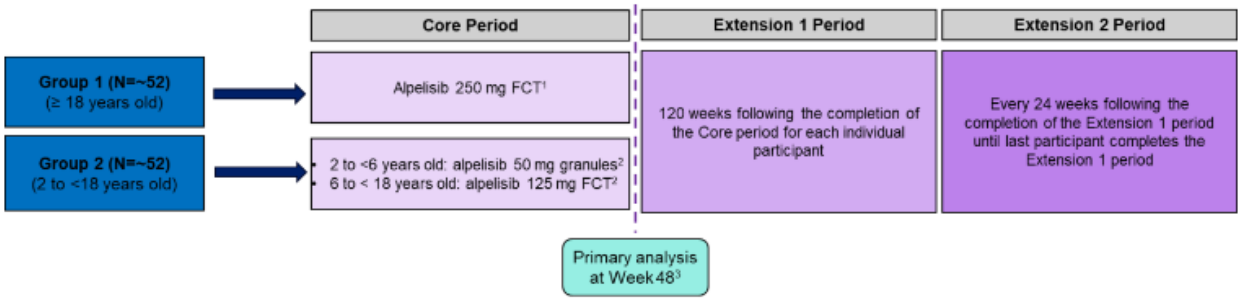
The applicant requested in the initial submission consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The Applicant considers the benefit-risk balance is positive in the following indication: 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.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant proposes to conduct as a specific obligation a Phase II single arm open-label, multi-center study to assess confirm the efficacy, safety and pharmacokinetics of alpelisib in paediatric and adult patients with PROS (EPIK-P4).

Figure 47 EPIK-P4 study design



1 Group 1: the starting dose is the maximum dose and therefore dose escalation is not allowed.
2 Group 2: dose escalation is permitted for participants ≥6 years of age after 12 weeks of study treatment up to 250 mg.
3 Occurs when all participants have reached Week 48 or discontinued earlier.

- the medicinal product fulfils an unmet medical need as there is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for this disease in the EU. Current management of these disorders consists of surgical procedures such as serial debulking (although regrowth often occurs after resection) or amputation, sclerotherapy, orthopaedic procedures to limit growth, endovascular occlusive procedures, and pain management. Patients with PROS have a significant unmet medical need for new and effective therapeutic approaches in the EU, including pharmacological treatments that aim to affect the root cause of PROS.

- The benefits of the medicine's immediate availability outweigh the risks inherent in the fact that additional data are still required.

The applicant discusses that a CMA would enable patients with severe and life-threatening manifestations of PROS, a condition with high unmet medical need and no approved pharmacological treatment in the EU, to access alpelisib. Alpelisib is currently not available to all patients in the EU with severe manifestations of PROS (neither under compassionate use nor via clinical studies) due to local regulations/restrictions or the patient's geographic location. Specifically, alpelisib treatment under compassionate use is not possible in some EU countries as local regulations do not allow for

compassionate use. Furthermore, although EPIK-P4 will be conducted in 7 European countries, (Austria, Belgium, France, Germany, Italy, Netherlands and Spain), study sites might not be readily accessible to all patients. As such, the applicant considers that a CMA for patients with severe or life-threatening manifestations would allow patients with an orphan disease and a significant need to have access to a treatment. Therefore, in light of the data from EPIK-P1, EPIK-P2 and EPIK-P3, the applicant concludes that the benefit to public health of the medicinal product's immediate availability on the market via a CMA outweighs the risks due to need for further data.

9.6.3.3.2. Discussion on the comprehensiveness of data in the context of a Conditional marketing authorisation

In regard to the request for a conditional Marketing authorisation, the CHMP considered that the following is to be accounted in terms of non-comprehensiveness of the dossier:

The available data are not considered comprehensive within the meaning of the CMA legislation due to the limitations in the pivotal study design (EPIK-P1), including the open-label, non-controlled design, data being retrieved from a retrospective chart review, a lack of an internal comparator and the small sample size; Supportive data also raise methodological issues (in EPIK-P3 there is a lack of standardisation in the follow-up and patients' evaluation for efficacy and EPIK P2 study is the only controlled study conducted with alpelisib in the treatment of PROS, included a broader population than the target population and used a different dosing regimen than the one intended for the approval and did not meet its primary efficacy endpoint).

In addition, no specific dose-response studies have been performed with alpelisib for the treatment of PROS. The doses currently proposed for marketing in both adults and paediatric patients are based on those used in the original compassionate use programme.

The absence of standardized data collection, the retrospective open label design of the study are prone to biases.

With respect to safety, the main uncertainty is related to the long-term use, including effects on growth, development and puberty.

These uncertainties are expected to be addressed as part of the specific obligation (EPIK-P4) imposed in the context of the conditional MA.

9.6.3.3.3. Conclusions and recommendation on conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease.

Indeed, PIK3CA-related overgrowth spectrum (PROS) is an umbrella term encompassing a diverse group of rare, phenotypically variable, disorders stemming from sporadic somatic gain-of-function mutations in the PIK3CA gene. PROS is characterized by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. The clinical impact of PROS depends on the anatomical site and extent of overgrowth and may include functional impairment (e.g. of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infection, impaired neurological development, seizures, thromboembolism, pulmonary hypertension, haemorrhage, as well as other manifestations that can be a consequence of overgrowth. The severity of PROS is highly variable, ranging

from localized overgrowth to severe, extensive, and life-threatening overgrowth affecting major vessels and/or critical organs. The target population in this application is adult and paediatric patients aged 2 years and older with severe or life-threatening manifestations of PROS who require systemic therapy.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive in 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. In light of the radiologic responses assessed by BRIC in the context of improved clinical outcomes at the patient level, efficacy of alpelisib in patients with PROS can be considered established. Furthermore, the safety profile is deemed acceptable and manageable through clinical management and routine risk minimisation measures.

- It is likely that the applicant will be able to provide comprehensive data through the specific obligation EPIK-P4, a Phase II single arm open-label, multi-center study conducted in order to confirm the efficacy, safety and pharmacokinetics of alpelisib in paediatric and adult patients with PROS and will be including a minimum number of severe or life-threatening participants. The proposed primary endpoint is the responder's rate define as confirmed ≥20% reduction from baseline in the sum of target lesion volume (1 to 3 target lesions) at week 48. The single-arm trial (SAT) design is considered acceptable considering the severe population and the ethical aspects raised by the AHEG.

The proposed SOB is considered sufficient to address the identified uncertainties and limitations and is expected to generate sufficiently comprehensive post-authorisation data on the efficacy and safety of alpelisib in the treatment of PROS.

- Unmet medical needs will be addressed, as there is currently no approved medical therapy for the treatment of severe or life-threatening manifestations of PROS in the EU. Current management of these disorders consists of surgical procedures such as serial debulking (although regrowth often occurs after resection) or amputation, sclerotherapy, orthopaedic procedures to limit growth, endovascular occlusive procedures, and pain management.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

It can be agreed that the benefits to public health of immediate availability on the market of alpelisib outweighs the risks, despite additional data are still required.

Indeed the availability aspects raised by the applicant and presented above are acknowledged.

Given the established potential for clinical benefit in patients with no other approved medical therapy, the known and manageable safety profile, the immediate availability provides a public health benefit that outweighs the risks associated with remaining uncertainties.

The CHMP considers the following measures necessary to address the missing data in the context of conditional marketing authorisation:

Specific obligations in relation to the CMA

Description	*Due date*
In order to further confirm the efficacy, safety and pharmacokinetics of alpelisib in the treatment of adult and paediatric patients with PIK3CA-related overgrowth spectrum (PROS), the MAH should submit the final results of the phase II single arm study CBYL719F12202 (EPIK-P4).	31 December 2032

9.7. Benefit-risk conclusions

9.7.1. At Day 210 –CHMP conclusions

In view of the data described above, the CHMP considers that the benefit-risk of Vijoice (alpelisib) in 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 is positive.