30 March 2023
EMA/506300/2023
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Vijoice

International non-proprietary name: alpelisib

Procedure No. EMEA/H/C/5468/0000

Note

Assessment report with all information of a commercially confidential nature deleted

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List of abbreviations

AE	Adverse event
AKT	Protein kinase B
ATU	Temporary Authorization for Use
BCDF	Baseline Clinical Data Form
BCRP	Breast cancer resistance protein
BMI	Body mass index
CI	Confidence interval
CLOVES	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
CRF	Case report form
CT	Computerized tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-drug interaction
DOR	Duration of response
DMC	Data Monitoring Committee
DRESS	Drug reaction with eosinophilia and systemic symptoms
eCRF	electronic Case Report Forms
DXA	Dual energy X-ray absorptiometry
ECOG	Eastern Cooperative Oncology Group
EM	Erythema multiforme
EMA	European Medicines Agency
FAO	Fibroadipose overgrowth
FDA	Food and Drug Administration
FCT	Film-coated tablet
FG	Fasting glucose
FIL	Facial infiltrating lipomatosis
FPFV	First patient first visit
FPG	Fasting plasma glucose
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HHML	Hemihyperplasia multiple lipomatosis syndrome
HRU	Healthcare resource use
HRQoL	Health-related quality of life
ICRR	Independent central radiology review
KTS	Klippel-Trenaunay syndrome
LON	lipomatosis of nerve
MAP	Managed access program
MCAP	Megalencephaly capillary malformation polymicrogyria
MCM	macrocephaly-capillary malformation
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NOAEL	no observed adverse effect level
PI3K	Phosphatidylinositol-3-kinase
PI3KCA	Gene which encodes the p110-α catalytic subunit of PI3K
PMC	Post-marketing commitment
PROS	PIK3CA related overgrowth spectrum

PT	Preferred term
RDI	Relative dose intensity
SAP	Statistical analysis plan
SD	Standard deviation
SJS	Stevens-Johnson syndrome
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUSARs	Suspected unexpected serious adverse reactions
TEN	Toxic epidermal necrolysis
U.S.	United States

CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for VIJOICE an orphan medicinal product in the treatment of adult and paediatric patients aged 2 years and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- The exact effect of alpelisib on tumour size is not known.
- Even when assuming there is an effect of alpelisib, reducing tumour size in some cases, it is not clear whether this translates into patient benefit.
- The effect of alpelisib on PROS phenotypes other than CLOVES is not clear. The long-term safety profile of alpelisib, notably its effects on growth and development in the paediatric population, is unknown.

1.1. Questions to be posed to additional experts

Proposed questions to be posed to the *ad hoc* expert group (AHEG):

1. The AHEG is invited to provide their view concerning whether the claimed responses, in their opinion, could be attributed to alpelisib or considered a chance finding.
2. If responses could be attributed to alpelisib in the AHEGs view, then the experts are invited to discuss whether benefit could be expected across the broad spectrum of PROS patients, regardless of the tissue affected and of the PROS phenotype.
3. Considering the ultra-rarity of the condition without any approved pharmacological treatment and with a high unmet medical need, the AHEG is invited to discuss if, in their opinion, the proposed confirmatory study EPIK-P2 would be feasible in the event that a CMA for alpelisib would be granted.

1.2. Inspection issues

1.2.1. GMP inspection(s)

Not applicable

1.2.2. GLP inspection(s)

All nonclinical data summarized in this nonclinical overview were submitted previously in support of the breast cancer indication (Piqray procedure number H0004804), with the exception of two additional GLP studies. These two rat male and female fertility studies (studies 2070119 and 2070120) are currently under assessment in variation EMEA/H/C/004804/II/13.

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.

1.2.3. GCP inspection(s)

Not applicable.

1.3. New active substance status

Based on the review of the data, it is considered that the active substance alpelisib contained in the medicinal product Vijoice is not qualified as a new active substance.

1.4. Additional data exclusivity / marketing protection

The applicant did not request consideration of one year data exclusivity or marketing protection in regards of this application.

1.5. 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 application did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Derogation(s) from market exclusivity

Not applicable.

2. Executive summary

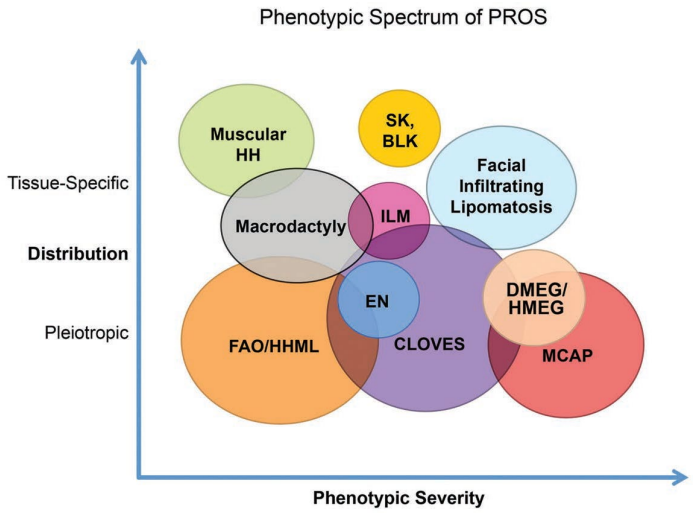
2.1. Problem statement

2.1.1. Disease or condition

Somatic activating mutations in PIK3CA gene, leading to a mosaic genotype, have been found to induce a spectrum of overgrowth and malformation disorders commonly known as "PROS".

PROS is considered as a group of syndromes resulting from a genetic alteration in the PIK3CA gene with diverse phenotypes, including (but not limited to): fibroadipose hyperplasia or overgrowth, hemihyperplasia multiple lipomatosis (HHML), congenital lipomatosis with overgrowth, vascular malformations, epidermal naevi, 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), and lipomatosis of nerve (LON), Klippel-Trenaunay syndrome (KTS) (Keppler-Noreuil et al 2015, Hughes et al 2020).

Figure 1 Phenotypic Spectrum of PROS: disorders have overlapping clinical features, some with tissue-specific, localized effects, some with pleiotropic and more severe manifestations.



Abbreviations: FAO/HHML, Fibroadipose Overgrowth/Hemihyperplasia-Multiple Lipomatosis; ILM, Isolated Large Lymphatic Malformation; CLOVES, Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal; EN, Epidermal Nevi; SK, Seborrheic Keratoses; BLK, Benign Lichenoid Keratoses; MCAP, Megalencephaly-Capillary Malformation; HMEG, Hemimegalencephaly; DMEG, Dysplastic Megalencephaly (Keppler-Noreuil et al 2015)

2.1.2. Epidemiology

The prevalence of PROS is difficult to estimate because of its rarity, its recent characterization (in 2014), variation in ascertainment, and the broad phenotypic spectrum (Mirzaa et al 2013, Keppler-Noreuil et al 2014). The estimated prevalence of the following five PROS conditions combined is about 14 per 1,000,000: CLOVES, MCAP syndrome, hemihyperplasia multiple lipomatosis, fibroadipose hyperplasia, and KTS. Notably, an increasing number of phenotypes has been included in PROS as a result of the identification of PIK3CA mutations in previously uncharacterized overgrowth syndromes (Gymnopoulos et al 2007, Madsen et al 2018, Venot et al 2018).

2.1.3. Biologic features aetiology and pathogenesis

PIK3CA associated overgrowth is typically not inherited. Somatic mutations occur during the post fertilization/zygotic phase of embryogenesis with most affected patients presenting with a pathogenic variant of PIK3CA. The somatic activating mutations in PIK3CA gene (coding for catalytic subunit, p110α, of the protein PI3K) and hyperactivation of the PI3K/AKT/mTOR pathway caused by these mutations lead to the development of heterogeneous mosaic segmental overgrowth disorders.

Overgrowth of cells in organs usually occurs with the onset of expression of certain growth factors during development (Suzuki et al 2017). While PIK3CA mutations can be detected across the entire coding sequence of the gene, 80% of the mutations are found in three major clusters namely glutamates (E) 542 and 545 in the helical domain and histidine (H) 1047 near the C terminus of the kinase domain. The profile of PIK3CA mutations in PROS closely resembles that in cancer, and these frequent mutations have been suggested to be associated with severe, focal overgrowth widely distributed but milder overgrowth (Gymnopoulos et al 2007, Madsen et al 2018, Venot et al 2018).

2.1.4. Clinical presentation, diagnosis

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 one year of age with progressive overgrowth of tissues persisting in some cases into adulthood.

The severity of PROS is highly variable, ranging from localized overgrowth, for example of a digit, to severe, extensive, and life-threatening overgrowth affecting major vessels and/or critical organs (Madsen et al 2018). PROS may be conceived of 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, skeletal and cardiac muscle can also be affected. Due to the extensiveness of vascular malformations and tissue overgrowth, PI3K-related syndromes pose a therapeutic challenge.

Functional impairment (e.g., of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infections can be a consequence of the overgrowth and can include impaired neurological development, seizures, thromboembolisms, pulmonary hypertension, and haemorrhages, amongst other manifestations all of which may be debilitating (particularly in the paediatric population), and may cause early mortality.

2.1.5. Management

There is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for the underlying disease in the EU. Current treatment comprises primarily of surgical debulking, along with orthopaedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure) which mainly addresses symptoms and complications of the disease. Most of the time these procedures require hospitalization, for management of associated co-morbidities. Depending on the type of procedure, co-morbidities may be mild (e.g., pain, nausea, vomiting, urinary retention, etc.) or severe (e.g., deep venous thrombosis, pulmonary embolism, bleeding, wound infections, etc). Regrowth following surgery occurs frequently and often requires repeated surgery indicating a clear unmet need for new therapeutic options for patients with PROS (Mirzaa et al 2013, Engel-Nitz NM et al 2021).

2.2. About the product

Alpelisib (BYL719) is α specific class I PI3K inhibitor belonging to the 2-aminothiazole 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.

Vijoice is intended for the treatment of adult and paediatric patients aged 2 years and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS).

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

The following interaction with the CHMP and National Scientific Advice (SA), Rapporteur, Co-

Rapporteur, and EMA pre-submission meetings were:

- AEMPS (Spain)- National Scientific Advice dated 10-Jul-2019
- ANSM (France)- National Scientific Advice dated 17-Sep-2019
- CHMP- Scientific Advice dated 27-Feb-2020
- CHMP- Initial Protocol Assistance dated 14-Oct-2021 (advice letter)
- EMA- written response to pre-submission meeting request received on 15-Jun-2022

Whenever available, the applicant provided the official meeting minutes/scientific advice letters issued by the respective Agencies.

In addition, a joint CHMP Rapporteur (France) and Co-Rapporteur (Spain) pre-submission meeting was held on 31-May-2022. The final minutes of the joint pre-submission meeting with the CHMP (Co)-Rapporteurs, reviewed and agreed by the CHMP (Co)-Rapporteurs, are not available at the time of the MAA submission.

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0536/2021 on the agreement of a paediatric investigation plan (PIP) that includes a deferral.

At the time of submission of the application, the PIP P/0536/2021 was not yet completed as some measures were deferred.

The PDCO issued an opinion on partial compliance for the PIP P/0536/2021 on 08-Mar-2022.

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

GMP

A declaration by the Qualified Person regarding GMP compliance of drug substance manufacturing sites has been submitted. This declaration is based upon direct audit of the active substance manufacturers.

GMP certificates were provided for the finished product manufacturing and primary packaging sites and for the sites responsible for batch release for EEA described below. Manufacturing authorisations were provided for the secondary packaging site.

GCP

The applicant states that CBYL719F12002 (Retrospective chart review) was designed, implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines and with the ethical principles laid down in the Declaration of Helsinki. Therefore, the structure of study report is based on available guidance, i.e., the GPP in section IV-D and the EMA Guideline on good pharmacovigilance practices (GVP) Module VIII for Post-authorization safety studies.

The applicant states two of the seven study sites participating in EPIK-P1, including Necker Hospital in France at which 44 of 57 (77%) of patients were enrolled, underwent pre-approval inspections by the FDA. No FDA Form 483 (Inspectional observations) was issued at either study site.

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

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

Vijoice is not included in the list of PRIME products on EMA website.

2.5.3. Accelerated assessment

The applicant did not request consideration of its application for an accelerated assessment

2.5.4. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

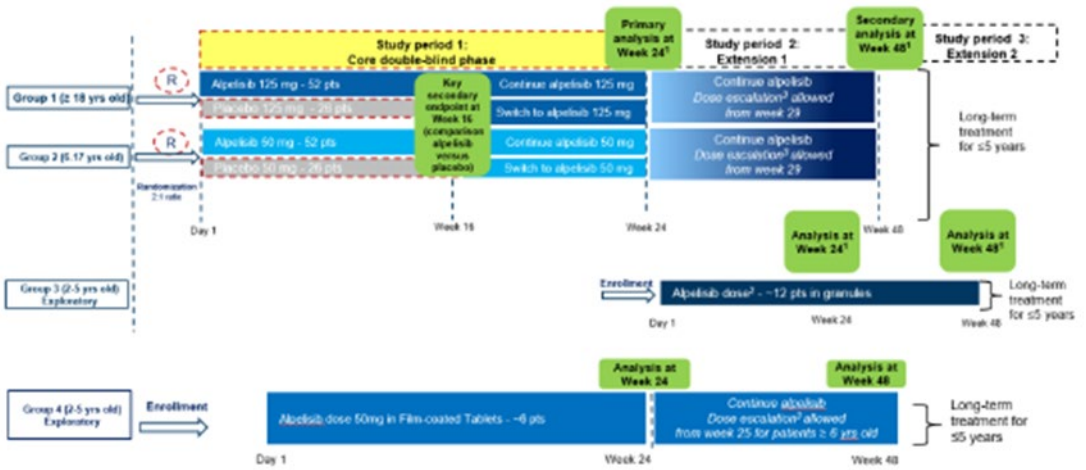
- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

In line with the current agreed alpelisib Paediatric Investigational Plan (PIP) decision (P/0536/2021; dated 03-Dec-2021), the applicant is conducting a prospective Phase II, double-blind study with an upfront, 16-week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics (PK) of alpelisib in paediatric (2–17 years) and adult patients with PROS (CBYL719F12201, referred to as EPIK-P2) with the intention to obtain the required comprehensive data.

The study is conducted in patients with PROS irrespective of disease severity. Patients will be enrolled with symptomatic and/or progressive overgrowth and at least one measurable lesion as confirmed by Blinded Independent Review Committee (BIRC) at baseline. As per the current protocol, the applicant plans to enroll participants in 4 groups according to participant age;

- Group 1: ≥ 18 years old (Film-coated tablets, FCTs),
- Group 2: 6 to 17 years old (FCTs),
- Group 3: 2 to 5 years old (granules)
- and Group 4: 2 to 5 years old (FCTs)

Figure 2 Study design of EPIK-P2



A total of approximately 156 participants with PROS will be enrolled across Groups 1 and 2 (N=78 participants per age group) and will be randomized in a 2:1 ratio to receive alpelisib (N=52 in each age group) or placebo (N=26 in each age group) during the first 16 weeks. Group 4 of approximately 6

participants will be enrolled in parallel and will receive alpelisib FCTs in an open label setting. After the primary analysis of Groups 1 and 2 at Week 24, the starting dose of alpelisib for Group 3 will be confirmed based on the efficacy, safety and PK data of Groups 1 and 2 in addition to the data from Group 4 as available. Group 3 will enrol approximately 12 participants treated with a new granule formulation.

The prospective EPIK-P2 study is currently ongoing and the overview of key milestones is presented below:

- First Patient First Visit (FPFV): 11-Apr-2021
- Number of patients enrolled as of 22-Jun-2022: 79 patients in total, 33 in Group 1 (patients ≥18 years of age treated with alpelisib tablets), 45 in Group 2 (6 to less than 18 years of age treated with alpelisib tablets), and 1 in Group 4 (2 to 5 years of age treated with alpelisib tablets)
- Planned completion of enrolment of Groups 1 and 2 (primary analysis): May-2023 (base case) / Dec-2022 (best case)
- Planned submission of primary analysis: Q2/Q3 2024 (base case)/ Q1 2024 (best case)
- Planned final clinical study report submission: 30-Sep-2030

• Unmet medical needs will be addressed.

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, orthopedic procedures to limit growth, endovascular occlusive procedures, and pain management. These interventions occur throughout the patients' early childhood and into adulthood (Keppler-Noreuil et al 2014). 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 to public health of the 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 manifestations of PROS, a condition with high unmet medical need and no approved pharmacological treatment in the EU, to get access to alpelisib. Alpelisib is currently not available to all patients in the EU with severe manifestations of PROS (neither under compassionate use nor via EPIK-P2) 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-P2 is being conducted in six of 31 European Economic Area (EEA) countries, namely Italy, France, Germany, Norway, Netherland and Spain, study sites might not be readily accessible to all patients even in these participating countries, or physicians may not be willing to include patients with severe disease in a study in which they may be randomized to treatment with placebo for 16 weeks. As such, the applicant considers that a CMA for patients with severe manifestations based on data from EPIK-P1 would allow a small subset of patients with an orphan disease and a significant need to have access to a treatment with a favourable benefit-risk ratio. Therefore, in light of the encouraging data resulting from EPIK-P1, 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.

2.5.5. Marketing authorisation under exceptional circumstances

The applicant did not request consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation.

2.5.6. Biosimilarity

Not applicable

2.5.7. Additional data exclusivity / marketing protection

The applicant did not request consideration of one year data exclusivity or marketing protection in regards of this application.

2.5.8. New active substance status

Not applicable.

2.5.9. Orphan designation

Alpelisib was designated as an orphan medicinal product EU/3/21/2420 on 26.3.2021 in the following condition: Treatment of PIK3CA related overgrowth spectrum.

2.5.10. Similarity with orphan medicinal products

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

2.5.11. Derogation(s) from orphan market exclusivity

Not applicable

2.5.12. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0536/2021on the agreement of a paediatric investigation plan (PIP) that includes a deferral.

At the time of submission of the application, the PIP P/0536/2021 was not yet completed as some measures were deferred.

The PDCO issued an opinion on partial compliance for the PIP P/0536/2021 on 08-Mar-2022.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as film-coated tablets for oral administration containing 50 mg, 125 mg and 200 mg of alpelisib as active substance.

Other ingredients are:

Tablet core: Cellulose microcrystalline, Mannitol, Sodium starch glycolate, Hypromellose, Magnesium stearate

Film coating: Hypromellose, Iron oxide, yellow (E172), Iron oxide, red (E172), applicable only to 50 mg and 200 mg strengths, Titanium dioxide (E171), Macrogol, Talc

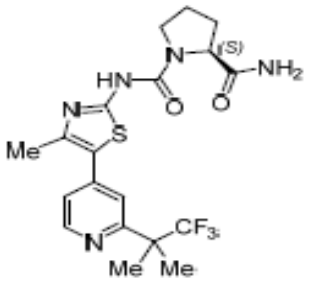
The product is available in PVC/PCTFE/alu blister packs.

3.1.2. Active Substance

The information provided for the alpelisib active substance is the same as the one approved for Piqray film-coated tablets EMEA/H/C/004804.

General Information

Alpelisib is a white to almost white powder, insoluble and practically insoluble in water, it has one stereogenic center, the absolute configuration is S, the molecule is used as single enantiomer. Alpelisib is considered slightly hygroscopic. Only one crystalline anhydrous form (Modification A) has been identified.



Manufacture, process controls and characterisation

The manufacturing process has been described adequately.

Input amounts in ranges are provided for reactants involved in the chemical transformation, reaction conditions and amounts of solvents process aids etc. are also informed.

Appropriate justification for choice of starting materials and their specifications has been provided. Discussion on impurities in the starting materials and their fate in the down-stream synthesis is presented in S.3.2.

Name and address of all the supplier of starting materials proposed has been provided. Specifications have been presented for each starting material/raw material.

The rationale for the selection of the starting materials is considered acceptable.

Specifications for the isolated intermediates are provided.

Manufacturing process development

A summary table is provided outlining the different synthetic pathways used during development and the used of the batches. Batch analysis results from batches manufactured according to the different synthetic pathways are included in 3.2.S.4.4.

The molecular structure has been satisfactorily characterized by Mass spectrum, UV, IR, 1H-NMR, 13C-NMR spectrum, X-ray crystallography, DSC.

The control strategy for mutagenic and potentially mutagenic impurities should still be reviewed.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Regarding reference standard it has been fully characterized by UV, H-NMR, C-NMR, mass spectrometry.

The active substance is primary packed into a low-density polyethylene (LDPE) bag and sealed. The sealed bag is placed into a second low density polyethylene (LDPE) bag, sealed and stored in a metal drum. The LDPE bags complies with ph. Eur. 3.1.3 and the EU food legislation on plastic materials and articles intended to come into contact with food.

Stability

The stability conditions are in agreement with ICH Q1A Guideline and the tests performed are considered stability indicating.

Stability studies for six pilot scale batches of alpelisib drug substance manufactured on another that than the site commercial site proposed were performed.

Results obtained up to 48 months at the long-term storage condition 30 °C/ 75%RH and 6 months at accelerated storage condition 40 °C/ 75%RH for the three drug substance batches manufactured at the proposed commercial manufacturing site are within specification for all of the quality characteristics tested.

The proposed retest period of 48 month for alpelisib drug substance when packaged as defined in Section [3.2.S.6] "Container closure system" and stored at a temperature below (up to) 30 °C, protected from light is acceptable.

The stability of the active substance under a series of different storage conditions/stress conditions has been examined; and it was concluded that the active substance is not stable in solution when exposed to hydrolytic, acidic, basic and oxidative stress conditions.

Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition of the product

The product is film-coated tablets for oral administration containing 50 mg, 125 mg and 200 mg of alpelisib. The description of the tablets can be found below:

				Imprint			
Strength	*Colour*	*Shape*	*Approximate size (mm)*	*One side*	*The other side*	*Beveled edges*	*Scored*
50 mg	Light yellow	Round and curved	7.2 (diameter)	"C7"	"NVR"	Yes	No
125 mg	Dark yellow	Ovaloid and curved	13.2 x 5.7	"Y7"			
200 mg	Pale yellow		16.2 x 6.5	"CL7"			

The tablet strengths can be differentiated by size, shape, colour and debossing between each other and with the Piqray EMEA/H/C/004804 50, 150 and 200 mg tablet.

The tablets are primary packaged in PVC/PCTFE/Alu blisters. These blisters are further assembled in cardboard-based packs.

Pharmaceutical development

Alpelisib (BYL719) 50 mg (light pink), 150 mg (pale red), and 200 mg (light red) film-coated tablets intended for oral administration are currently approved for the treatment of patients with breast cancer in the EU (Piqray®, EU/1/20/1455). A differentiated product, alpelisib 50 mg (light yellow), 125 mg (dark yellow), and 200 mg (pale yellow) has been developed for the treatment of patients with PROS (PIK3CA-related overgrowth spectrum). The 125 mg (dark yellow) strength was developed as a bracketed strength between alpelisib 50 mg and 200 mg film-coated tablets (yellow shades) to facilitate dose modifications and provide convenience for patients.

There are no changes to the alpelisib drug substance used for Piqray® tablets and alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades).

The excipients utilized in the tablet cores of alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades) are same as those used in Piqray® tablets. The only change in the qualitative composition is in the pigments used in the non-functional film-coating. The coating premix black was used for Piqray® tablets while coating premix yellow is used for alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades). However, both the coating premixes (coating premix black and coating premix yellow) contain the same base ingredients hypromellose, polyethylene glycol 4000 and talc, differing only in the pigment utilized (black color is achieved by iron oxide black and yellow color is achieved by iron oxide yellow).

Information on batches used in the clinical studies was provided.

The product information states that the tablet may be dispersed in 50 to 150 ml water.

The dissolution method is considered acceptable.

According to the SmPC section 6.6 for pediatric patients who are not able to swallow tablets, the tablets may be crushed and given as a suspension in water. The SmpC section also specifies:" Discard the oral suspension if it is not administered within 60 minutes after preparation". The chemical stability and compatibility of an oral suspension of disintegrated film-coated tablets in water was demonstrated after storage in water for up to 1 hour in cups. The SmPC statement is justified.

Manufacture of the product and process controls

Manufacturers

Valid GMP certificates were provided for the manufacturing and primary packaging sites and for the sites responsible for batch release for EEA.

Manufacturing authorisations were provided for the secondary packaging site.

Manufacturing process

Film-coated tablets are manufactured by a standard process consisting in the following steps: wet granulation, wet milling, drying, blending, compression, film coating and packaging.

In the batch formula, name, quantity and reference to the quality standards of all ingredients used in the course of the manufacture are stated. Proposed batch sizes are defined (in bulk size and number of tablets).

A flow chart and a narrative description of the manufacturing process are provided. The following issues are described: equipment type, manufacturing process principle, steps of the process, in-process controls, where materials enter the process -with batch size(s)- and process parameters (with target values or ranges). Critical steps, including in-process controls, test methods and acceptance criteria are provided. There are no isolated intermediates.

Validation of the bulk product hold time is provided. A shipping evaluation study is also performed.

The expiration period of a batch is calculated in accordance with the EU guideline Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96).

Process validation was performed on three batches each for alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades). The validation batches were successfully manufactured within the valid process parameter settings and operational ranges presented.

Product specification, analytical procedures, batch analysis

Parameters included in the specification cover all the critical aspects for ensuring the quality of the drug product and guaranteeing safety and efficacy and are the same as the one approved for Piqray 50 mg and 200mg tablets except for the appearance. Analytical methods are sufficiently described.

Results from 3 pre-validation batches and 3 validation batches of each strength have been provided. Batch results support a consistent production and the proposed specifications.

A risk assessment based on the general principles outlined in the ICH Q3D guideline was performed for Piqray® to assess the potential presence of elemental impurities in Piqray® 50 mg, 150 mg, and 200 mg film-coated tablets. This risk assessment and data also support alpelisib 50 mg, 125 mg and 200 mg film-coated tablets (yellow shades).

A risk assessment of formation of and contamination of N-nitrosamines is presented. Based on this evaluation, the conclusion is the same as the conclusion for Piqray tablet, there is no risk for the presence of N-nitroso compounds in alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades).

The primary packaging for alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets consists of PVC/PCTFE/alu blister packs. The plastic material is compliant with the EU Commission Regulation nº 10/2011 on plastic materials and articles intended to come into contact with food.

Stability of the product

Stability studies have been performed on 3 batches of each strength of alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades) manufactured by the commercial site. The studies were performed according to the guideline ICH Q1A (CHMP/ICH/2736/99) and include testing of those attributes that are susceptible to change during storage and are likely to influence safety and/or efficacy. The analytical methods have been correctly validated and are stability-indicating. The container closure system is the same packaging proposed for storage and distribution.

Accelerated testing has been concluded for all the tested batches. All batches complied with the specifications for all the quality characteristics tested. Data up to 18 months are available for all the

tested batches at long term 25°C/60% RH and 30°C/75% RH storage conditions. All batches complied with the specifications for all the quality characteristics tested.

A full stability program up to 36 months has been completed for Piqray®50 mg, 150 mg, and 200 film-coated tablets.

The applicant consider that the Piqray stability data also support alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades).

The proposed shelf-life is 36 months without storage precaution is considered acceptable.

Post approval change management protocol(s)

Not applicable

Adventitious agents

None of the material used in the formulation of alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades) is of human or animal origin.

Magnesium stearate used is of vegetable origin.

GMO

Not applicable

3.1.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Based on the review of the quality data provided, the Rapporteur considers that the marketing authorisation application for alpelisib 50 mg, 125 mg, and 200 mg film-coated tablets (yellow shades) could be approvable from the quality point of view provided that satisfactory answers are given to the "other concerns" as detailed in the List of Outstanding issue. Failure to resolve other concerns may render the application not approvable.

3.2. Non-clinical aspects

3.2.1. Introduction

All non-clinical studies submitted by this applicant were already evaluated to support of the breast cancer indication (see EMA/H/C/004804 – PIQRAY – same applicant as VIJOICE), with the exception of the additional *in vivo* pharmacology studies (Venot et al 2018), 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). For clarity/ completeness, data obtained in these already assessed studies were summarized as well as the newly submitted studies.

3.2.2. Pharmacology

All pharmacodynamics studies submitted by this applicant were already evaluated to support of the breast cancer indication (PIQRAY, procedure EMEA/H/C/004804). No additional *in vitro* primary PD, secondary PD or safety pharmacology studies were submitted. Characterization of alpelisib *in vivo* PD activity was updated mainly with one literature reference (Venot et al 2018) in a mouse model of

PROS/congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES), which partially recapitulates human disease. This is acceptable.

3.2.2.1. Primary pharmacodynamic studies

In vitro activity

In vitro studies with alpelisib appears to show that alpelisib is α 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 lacked activity against the class III family member Vps34, the PIKKs mTOR, DNA-PK and ATR (IC_{50}>9100 nM), other 38 tyrosine and 27 serine/threonine-specific kinases (IC_{50}>10μM) and was significantly less potent against the distinct lipid kinase PIK4β (IC_{50}=581 nM) and cABL (IC_{50}=2000 nM).

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

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

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

In vivo activity

As already mentioned in PIQRAY submission, 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. In theory, clinical efficacy data will supersede the non-clinical PD data. Although no additional non-clinical study will be requested, this study do not reassure the doubts raised by submitted clinical efficacy data (see clinical section). From non-clinical perspective, this issue will be not further pursed.

3.2.2.2. Secondary pharmacodynamic studies

No new study were submitted, the secondary pharmacodynamic studies were already assessed in previous alpelisib submission (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 was found with batch NX-1 but was not confirmed with batch NX-2. Weaker pharmacology activity was also found on the adenosine Ad1 receptor (15 µM, Ki=13 µM) and the phosphodiesterase PDE4d (13 µM). IC_{50} values found are all around 1000 fold or more 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.

3.2.2.3. Safety pharmacology programme

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

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

Alpelisib had an IC_{50} value of 9.4 µM in the hERG assay. An update of exposure margin need to be submitted by the applicant based on the intended posology in PROS indication. Given the current uncertainties of the Applicant's PK exposure predictions (see clinical D150 JAR – PK part), it is preferable to adopt a more conservative approach, and therefore to rely on the wording set during PIQRAY procedure (see proposed modification in PI document) and to not mention the multiple of exposure in paediatric patients. These margins of exposure will be updated in a future MAA type II variation.

Although, no treatment-related ECG effects in dog were noted within 2 and 4 and 13-week repeated oral dose toxicity studies up to 90 mg/kg/day and rising-dose study up to a dose of 180 mg/kg/day, an *in*

vivo telemetry study in dogs showed an elevated blood pressure, at doses starting from 5 mg/kg, which is lower than the estimated 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.

3.2.2.4. Pharmacodynamic drug interactions

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

3.2.3. Pharmacokinetics

The animal PK profile of alpelisib was characterized and assessed in the previous MAA for PIQRAY (procedure EMEA/H/C/004804). No additional studies are submitted in the current submission. This is acceptable. For clarity/completeness, data obtained in these studies were 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 Cmax in dogs.

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

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

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

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

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

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

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

3.2.4. Toxicology

All toxicity studies submitted by this applicant were already evaluated to support of 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).

Originally alpelisib was intended for the treatment of advanced cancers; therefore, the toxicology program had been designed in accordance with ICH S9 guideline. However, treatment of PROS patients is a non-oncology therapeutic. This intended indication is outside the scope of ICH S9 (Q&A - ICH S9 guideline on nonclinical evaluation for anticancer pharmaceuticals, question 1.4 page 5/17, EMA/CHMP/ICH/453684/2016). No long-term animal studies have been performed. An ongoing 2-year carcinogenicity study is ongoing to complete the non-clinical package. Even if current requested indication mentioned patients with severe manifestations, it does not imply that it is a life-threatening disease for all concerned patients. Although long-term safety information in PROS patients are currently classified at missing information (RMP) and the need of additional results (EPIK-P2 and EPIK-P3) are currently reinforced (see clinical AR – safety part), the current clinical experience could be considered sufficient to supersede the missing long-term non clinical studies. It is noted that a 2-year carcinogenicity study is ongoing, and therefore no other long-term animal studies will be requested.

3.2.4.1. 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 diarrhea was seen at ≥ 90 mg/kg. No treatment-related effects on electrocardiographic parameters was seen and no deaths occurred at any dose level.

3.2.4.2. Repeat dose toxicity

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 a 8 week recovery period.

In 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 in connection 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; however, the table of interspecies comparison was not corrected. 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.

Repeat-dose toxicity studies in dogs was 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 dog 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 dog, 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.

3.2.4.3. Genotoxicity

Standard battery for alpelisib were performed according 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 the rat. Alpelisib was negative *in vitro* and *in vivo*. Toxicokinetics showed that rats were exposed at clinically relevant doses. In conclusion, no studies indicated a genotoxic potential of alpelisib at clinically relevant doses.

3.2.4.4. Carcinogenicity

A 2-year carcinogenicity rat study is ongoing; this is reflected in the SmPC section 5.3 .

3.2.4.5. Reproductive and developmental toxicity

Fertility study (2070119) showed that alpelisib did not affect male reproductive indices in nonclinical species (including mating, fecundity, or fertility indices). However, reproductive and fertility endpoints were affected at exposure levels at or below the recommended human dose, such as accessory glands weight (seminal vesicles and prostate). These findings correlated with atrophy and/or reduced secretion in prostate and seminal vesicles, respectively. Similar effects were noted in repeat dose toxicity studies at clinically relevant doses based on AUC. As such, as a conservative measure, the affected endpoints are considered as potential predictors of impaired male fertility, and reflected in the SmPC.

Embryo-foetal development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity. In rats and rabbits, following prenatal exposure to alpelisib, increased incidences of pre- and post-implantation losses, reduced foetal weights and increased incidences of foetal abnormalities (enlarged brain ventricle, decreased bone ossification and skeletal malformations) were observed starting at exposures within those in humans at the highest recommended dose of 250 mg in adult patients, indicating potential clinical relevance. A revision of the text has been requested for SmPC 5.3, since it is viewed as potentially misleading in the absence of actual data for the paediatric population. Indeed, it indicated that these adverse developmental effects were seen starting at exposure levels above those in humans at the recommended 50 mg dose in paediatric patients. However, there is currently no pharmacokinetic data in children, and exposure levels in patients from 2 years were derived from preliminary population PK analysis on adult cancer patients presenting a number of assumption and limitations. In addition, adolescent females of childbearing potential could be treated at doses up to 125 mg/day according to the dose escalation scheme proposed in SmPC 4.2 for patients ≥6 years of age. Given the current uncertainties of the Applicant's PK exposure predictions (see clinical D150 JAR – PK part), it is preferable to adopt a more conservative approach, and therefore to rely on the wording set during PIQRAY procedure (see proposed modification in PI document) and to not mention the multiple of exposure in paediatric patients. These margins of exposure will be updated in a future MAA type II variation.

No juvenile toxicity study was conducted with alpelisib, in line with the paediatric investigation plan adopted for the treatment of PROS in patients from 2 to 18 years of age (EMA decision P/0329/2020). In repeat-dose toxicity studies, degenerative effects seen in incisors and some growth plates of bones in rats were noted. Since this could be of relevance for this paediatric population, these effects are mentioned in SmPC section 5.3. According to the RMP, regular monitoring of the growth and development of pediatric patients treated with alpelisib is advised and will be performed in prospective clinical studies.

3.2.4.6. Toxicokinetic data

Interspecies comparison

The recommended human dose (RHD) is 250 mg/day for adult PROS patients (18 years old and above) and 50 mg/day for paediatric PROS patients (2-17 years old) with a possible dose escalation scheme proposed for patients ≥ 6 years of age at 125 mg/day. In comparison, for the breast cancer indication, the approved dose is 300 mg/day for adult patients. Therefore, alpelisib systemic exposure ratios in toxicity studies were updated in the non-clinical package and reported in the SmPC section 5.3. Currently, no PK data in adult (18 years old and above) or paediatric (2-17 years old) patients with PROS are available. PK parameters in PROS adults and children will be generated in the ongoing clinical trials (EPIK P2 and EPIK P3). Presently, the following adult exposure was selected to update the exposure ratios: steady state $AUC_{0\text{-}24h}$ = 21900 ng.h/mL following repeat daily dosing of 250 mg; this adult exposure was measured in cancer patients (clinical study CBYL719Z2102). The predicted exposure in PROS patients at 2 years of age following 50 mg dose (6000 ng.h/mL; as measured by steady state $AUC_{0\text{-}24h}$) was based on a preliminary population PK analysis on adult cancer patients treated with alpelisib; however, there

were number of assumptions and limitations (see clinical AR – section PK), limiting therefore the overall confidence in this exposure value. Moreover, there is no exposure level predicted at the dose of 125 mg/day which could be proposed for patients ≥ 6 years of age. In view of the above mentioned uncertainties, low ratios reported for paediatric patients could be considered as within the clinical exposure levels. Given that the current uncertainties of the Applicant's PK exposure predictions (see clinical D150 JAR – PK part) persist, it is preferable to adopt a more conservative approach, and therefore to rely on the wording set during PIQRAY procedure (see proposed modification in PI document) and to not mention the multiple of exposure in paediatric patients. These margins of exposure will be updated in a future MAA type II variation.

3.2.4.7. Tolerance

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

3.2.4.8. Other toxicity studies

Metabolites

The most prominent plasma metabolite in human was BZG791 which represented 26.7% of total ^{14}C AUC (measured in adults). No pediatric PK parameters are available to discuss the BZG791 in children; however, since alpelisib could be administrated in children starting from 2-year 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 (but not in dog). 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 toxicology studies according the requirements described in ICH guideline M3 (metabolite above 10%). It is unfortunate that the Applicant has not provided any discussion on the presence metabolite in the current ongoing rat carcinogenicity study or any indication of tested doses in this study. Given the absence of these data, results from the 2-year carcinogenicity study will be taken into account for the adequacy/validity of exposure levels.

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 (N,O-dimethylhydroxylamine, WDZ193, OZG328) were tested positive in the non-GLP AMES tests. Three impurities (BYL719-D6, WEB679, PGO385) 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. In line with the ICH M7 Q&A document, the QSAR reports (for all impurities where a QSAR prediction was performed) should be incorporated in module 4.

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). However, as two in vitro 3T3 NRU phototoxicity tests (OECD TG432, non-GLP/GLP) did not identify a relevant phototoxicity potential for alpelisib, it is concluded that alpelisib does not seem to be phototoxic.

Investigative studies (skin toxicity)

Follow-up rat studies to investigate mechanism of skin rashes (studies 1770766 and 1870156) confirms the results already obtained in 4-week oral (gavage) investigative skin toxicity study in female Brown Norway rats (study 1670271) which was previously assessed in PIQRAY procedure. The mechanism of skin toxicity need 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.

3.2.5. Ecotoxicity/environmental risk assessment

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

Summary of main study results

Substance (INN/Invented Name): Alpelisib (chemical name: (2S)-1-N-{4-Methyl-5- [2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl} pyrrolidine-1,2-dicarboxamide)			
CAS-number (if available): 1217486-61-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Pow at pH 5 = 3.04 log Pow at pH 7 = 3.03 log Pow at pH 9 = 3.03	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	1.71 L/Kg (low dose) 2.05 L/kg (high dose)	Not bioaccumulative
Persistence	DT50 or ready biodegradability	$DT_{50\ (sediment,\ 12\ ^oC)}$ = 186 d $DT_{50\ (total\ system,\ 12\ ^oC)}$ = 138d	vP
PBT-statement :	The compound is not considered as PBT nor vPvB		
Toxicity	CMR	Reprotoxicity	T
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	2.75	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc sludge = 263 mL/g and 525 mL/g Koc soil = 1642 mL/g, 3873 mL/g and 1087 mL/g	Average Koc sludge = 2201 mL/g
Ready Biodegradability Test	OECD 301	No significant biodegradation. Not readily biodegradable.	~~P~~
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 (water, 12°C) = 15.8 – 19.7 days DT90 (water, 12°C) = 65.5– 110.0 days	vP in sediment, P in total system

		DT50 (sediment, 12°C) = 107.0 – 186.0 days DT90 (sediment, 12°C) = 354.0 – 617.0 days DT50 (total system, 12°C) = 47.4 – 138.0 days DT90 (total system, 12°C) = 158.0 – 459.0 days Shift into sediment 51.5% (day 14), 46.1%parent + 5.4%NER) Transformation products >10%: 1. TP1 (NVP-BZG791): max. 10.6%/ 36.9% (day32) 2. TP3 (5-(2-tert-butyl-pyridin-4-yl)-4-methyl-thiazol-2- ylamine): max. 11.5%/ 38.6% (d102)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	72h-NOEC	5.6	mg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD 211	21d-NOEC	0.48	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	30d-NOEC	0.30	mg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	3h-NOEC	1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	$BCF_{kinetic}$	1.71 2.05	L/kg	Not bioaccumulative 5% lipid normalised and growth corrected
Sediment dwelling organism	OECD 218	28d-NOEC	64	mg/kg	*Chironomus riparius*, organic carbon 2.1%

3.2.6. Discussion on non-clinical aspects

All non-clinical studies submitted by this applicant were already evaluated to support of the breast cancer indication (see EMA/H/C/004804 – PIQRAY – same applicant as VIJOICE), 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). One literature reference was added to characterize alpelisib *in vivo* PD activity in PROS population.

As previously described, *in vitro* studies support alpelisib is a specific p110α inhibitor and inhibits the effects mediated by this kinase as phosphorylation of AKT and AKT downstream effectors (GSK3β and p70S6K). Moreover alpelisib showed markedly selective efficacy in PIK3CA mutated cell lines when compared to will-type cell lines and when compared to pan-PI3K inhibitors. In biochemical assays, BZG791, the primary circulating metabolite of alpelisib, was over 500 fold less potent than alpelisib on p110α, over 4 fold less potent than alpelisib on the other class I PI3K lipid kinases and, similar to alpelisib,

BZG791 was not active on Vps34 and mTOR. Mechanistic cell-based assays confirmed BZG791 shows no activity on the p110α, p110β and p110δ isoforms.

Pharmacology *in vivo* studies supported the tumor volume reduction based on mouse model of PROS/congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES), which partially recapitulates human disease. 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. In theory, clinical efficacy data will supersede the non-clinical PD data. Although no additional non-clinical study will be requested, this study do not reassure the doubts raised by submitted clinical efficacy data (see clinical section). From a non-clinical perspective, this issue will be not further pursed.

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

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

Based on the hERG inhibition seen *in vitro* but the absence of any *in vivo* signal, the results of the cardiovascular safety pharmacology studies, indicate a negligible risk of an electrophysiological effect of alpelisib. However, alpelisib caused an increase in blood pressure and a persistent decrease in average heart rate. Description of this findings are correctly reported in the SmPC but it is preferable to adopt a more conservative approach, and therefore to rely on the wording set during PIQRAY procedure given that the uncertainties of the Applicant's PK exposure predictions still persist.

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

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

The toxicity of alpelisib after repeated oral administration was studied in rats and dogs with dosing up to 13 weeks. The pharmacodynamic target and the major pathways of alpelisib metabolism in humans were all represented in these species. Thus the choice of rats, and dogs was appropriate for the toxicity evaluation of alpelisib. Originally alpelisib was intended for the treatment of advanced cancers; therefore, the toxicology program had been designed in accordance with ICH S9 guideline. However, treatment of PROS patients is a non-oncology therapeutic. This intended indication is outside the scope of ICH S9 (Q&A - ICH S9 guideline on nonclinical evaluation for anticancer pharmaceuticals, question 1.4 page 5/17, EMA/CHMP/ICH/453684/2016). No long-term animal studies have been performed. An ongoing 2-year carcinogenicity study is ongoing to complete the non-clinical package. Even if current requested indication mentioned patients with severe manifestations, it does not imply that it is a life-threatening disease for all concerned patients. Although long-term safety information in PROS patients are currently classified at missing information (RMP) and the need of additional results (EPIK-P2 and EPIK-P3) are currently reinforced (see clinical AR – safety part), the current clinical experience could be considered sufficient to supersede the missing long-term non clinical studies. It is noted that a 2-year carcinogenicity study is ongoing, and therefore no other long-term animal studies will be requested.

In the rat, and dog repeated-dose toxicity studies, 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. Most toxicologically relevant

changes can be considered to be associated with the pharmacological activity of alpelisib as an agent that inhibits the proliferation or maintenance of rapidly dividing tissues (hematopoietic, lymphopoietic, gastrointestinal systems, the skin, adnexal tissues, the teeth and bones).

Currently, no PK data in adult or paediatric patients with PROS are available. Alpelisib systemic exposure ratios in adult PROS patients were updated based on measured systemic exposure in cancer patients at 250 mg/day determined in clinical study CBYL719Z2102. This is currently acceptable. Based on the calculated safety margins with this extrapolated exposure (<1), adverse events in rats and dogs occurred at therapeutic plasma levels or below. However, alpelisib systemic exposure ratios in paediatric PROS patients were calculated from preliminary population PK analysis which presented number of assumptions and limitations. Moreover, patients ≥ 6 years of age could start at 50 mg/day and then the dose could be increased at 125 mg/day with no predicted exposure level. In view of the above mentioned uncertainties, low ratios reported for paediatric patients could be considered as within the clinical exposure levels. Given that the current uncertainties of the Applicant's PK exposure predictions (see clinical D150 JAR – PK part) persist, it is preferable to adopt a more conservative approach, and therefore to rely on the wording set during PIQRAY procedure (see proposed modification in PI document) and to not mention the multiple of exposure in paediatric patients. These margins of exposure will be updated in a future MAA type II variation. A commitment is requested (**LoOI**).

No studies indicated a genotoxic potential of alpelisib at clinically relevant doses. A 2-year carcinogenicity rat study is ongoing; this is reflected in the SmPC section 5.3.

In newly submitted fertility study (studies 2070119 and 2080120), no alpelisib-related effect on male fertility and reproductive performance, sperm parameters, and testicular histology were seen at doses up to 20 mg/kg/day (~2-fold the clinical exposure based on toxicokinetics data of the 13-week toxicity study). Nevertheless, inhibitory effects were consistently induced by alpelisib across species in fertility relevant organs such as testes, prostate or seminal vesicles in nonclinical studies. The sensitivity of mating trials to fertility effects in rodents is low given the extremely high production of sperm in this species and the fact that these animals remain fertile even with reductions in sperm of up to 90% (Mangelsdorf et al., 2003). Whereas smaller reductions in fertility parameters in humans could have a more significant effect on fertility. Also, this drug has shown an effect on accessory organs which are in themselves indicators of a potential fertility effect. Overall, it is recommended to adopt a conservative approach and report potential liabilities for male subjects accordingly in SmPC.

No juvenile toxicity study was conducted with alpelisib, in line with the paediatric investigation plan adopted for the treatment of PROS in patients from 2 to 18 years of age (EMA decision P/0329/2020). In repeat-dose toxicity studies, degenerative effects seen in incisors and some growth plates of bones in rats were noted and could be of relevance for this paediatric population and have therefore been reported in SmPC 5.3. According to the RMP, regular monitoring of the growth and development of pediatric patients treated with alpelisib is advised and will be performed in prospective clinical studies.

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

The most prominent plasma metabolite in human was BZG791 which represented 26.7% of total ^{14}C AUC (measured in adults). BZG791 was adequately assessed in the toxicology studies according the requirements described in ICH guideline M3. It is unfortunate that the Applicant has not provided any discussion on the presence metabolite in the current ongoing rat carcinogenicity study or any indication of tested doses in this study. Given the absence of these data, results from the 2-year carcinogenicity study will be taken into account for the adequacy/validity of exposure levels.

Alpelisib does not seem to be phototoxic. Follow-up rat studies to investigate mechanism of skin rashes (studies 1770766 and 1870156) confirms the results already obtained in 4-week oral (gavage)

investigative skin toxicity study in female Brown Norway rats (study 1670271) which was previously assessed in PIQRAY procedure. The mechanism of skin toxicity need 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.

According to the specifications, three impurities (BYL719-D6, WEB679, PGO385) 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. In line with the ICH M7 Q&A document, the QSAR reports (for all impurities where a QSAR prediction was performed) should be incorporated in module 4.

ERA

Alpelisib is not expected to pose a risk to the environment.

3.2.7. Conclusion on non-clinical aspects

There are no major objections on the non-clinical parts precluding a marketing authorisation of alpelisib. However, three outstanding issues that need to be addressed have been identified.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Study Code	Study objective / population	No. of treated subjects	Formulation	Dose / Regimen & Food Status
Biopharmaceutical studies				
[Study A2103] (Food effect & ranitidine DDI)	Single-center, open-label, randomized, five period, ten sequence crossover study to investigate the singular and joint effect of food and the histamine H2-receptor antagonist ranitidine on the PK of oral alpelisib in healthy subjects	21	Formulation D	SD 300 mg Fasted & fed
[Study X1101] (Food effect)	Exploratory, randomized, 2 period, 2 sequence crossover food effect expansion/ Japanese subjects with advanced solid tumors whose tumors have an alteration of the PIK3CA gene	8 (6 completed)	Formulation B/C	RD 350 mg Fasted & fed
[Study A2109]	Single-center, 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 (30 completed) Cohort 2: 74 (71 completed)	Formulation D/E	SD 200 mg Fasted & Fed
Mass balance (hADME)				
[Study X2107] (hADME)	Single-center, open-label study to investigate the Absorption, Distribution, Metabolism and Excretion (ADME) of alpelisib in healthy subjects	4	Radiolabeled drug in hard gelatin capsule	SD 400 mg Fasted
Special populations study				
[Study A2105] (Hepatic Impairment)	Phase 1, open-label, single-dose, multicenter, parallel group study to assess pharmacokinetics of and safety of alpelisib (BYL719) in subjects with moderate and severe hepatic impairment (based on Child-Pugh) compared to matched healthy subjects	**Total: 23** Hepatic impairment subjects: 6 each + 11 matching healthy subjects	Formulation D	SD 300 mg Fasted

Drug-drug interaction studies				
[Study Z2102] (Everolimus DDI)	Phase Ib dose-finding, open label safety and tolerability study of the combination of alpelisib and everolimus (and exemestane) in subjects with advanced solid tumors (Alpelisib as a potential perpetrator of a CYP3A4)	25 subjects dosed with everolimus and alpelisib 250 or 300 mg	Formulation D	RD 250 or 300 mg q.d. Fed
[Study 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	All 25 subjects dosed with rifampin and alpelisib 300 mg	Formulation E	RD 300 mg q.d. Fed
[Study 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 (28 completed)	Formulation E	RD 300 mg q.d Fed
Single agent PK studies in subjects with solid cancers				
[Study X2101] (First-in-human)	Phase Ia, multicenter, open-label dose escalation study of oral alpelisib in adult subjects with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene	134 single agent in solid tumors	Formulation A, B, and C	RD 30-450 mg q.d. & 120-200 mg b.i.d. Fed
[Study X1101]	Phase I dose-escalation study of alpelisib in Japanese subjects with advanced solid tumors	25	Formulation B and C	RD 90-400 mg q.d. Fasted and Fed
Combination PK studies with fulvestrant in subjects with advanced breast cancer				
[Study X2101]	Phase Ia expansion arm in combination with fulvestrant in HR+, HER2- aBC after multiple lines of therapy	87	Formulation A, B, and C	RD 300, 350, 400 mg q.d. Fed

[Study C2301] (SOLAR-1)	Phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with HR+, HER2- aBC which progressed on or after aromatase inhibitor treatment	572	Formulation D	RD 300 mg q.d. Fed
Combination PK studies with cetuximab in subjects with recurrent or metastatic head and neck squamous cell carcinoma				
[Study X2104]	A Phase Ib dose escalation/randomized Phase II, multicenter, open-label study of BYL719 in combination with cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma	45	Formulation B, C, and dispersible tablet	Arm A: 300, 400 mg FCT q.d Arm B: 300 mg crushed FCT as an oral suspension q.d Arm C: 300 mg dispersible tablets via G-tube q.d

hADME: human Absorption, Distribution, Metabolism and Excretion; SD: single dose administration; RD: repeated dose administration; aBC: advanced breast cancer, FMI: final market image; HR+: hormone-receptor positive; HER2-: human epidermal growth factor receptor 2 negative; b.i.d: twice a day; DDI: drug-drug interaction; q.d: once daily

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

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

Alpelisib in combination with fulvestrant is indicated for the treatment of postmenopausal 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. The recommended dose is 300 mg alpelisib (2x 150 mg tablets) taken once daily immediately after food.

In Europe, Alpelisib was approved on 27-Jul-2020 under the brand name of Piqray®. Three strengths of film-coated tablets (FCT) are available: 50; 150 and 200 mg.

In the current submission, the applicant seeks a market approval 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). The proposed dosing regimen is:

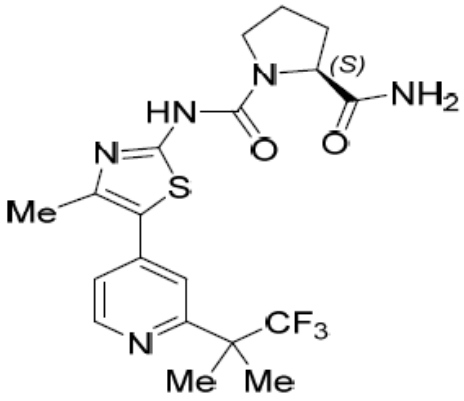
- 250 mg orally, taken once daily in adults patients, and
- 50 mg orally, taken once daily in paediatrics patients (2 to less than 18 years of age) with a dose increase to 125 mg that should be considered in children ≥6 years old for response optimisation after 24 weeks of treatment

The drug product for registration is a film-coated tablet proposed at 3 strengths: the two same 50 and 200 mg already commercialized and a new FCT of 125 mg (instead of the 150 mg strength).

Alpelisib has a molecular weight of 441.47 Da. The molecular formula is C19H22f3N5O2S and the chemical structure of the drug substance is presented in

Figure 3.

Figure 3: Chemical structure of Alpelisib



For the PROS indication, alpelisib was initially used in France as part of a compassionate use (CU) program. A retrospective non-interventional medical chart review study (referred to as **EPIK-P1**) was then conducted, including patients 2 years of age and older.

Of importance, no PK sampling was performed in patients with PROS receiving alpelisib in study **EPIK-P1**. Thus, no new PK information in the target PROS population are provided in support of this submission (in comparison to those previously reported in the breast cancer MAA). However, according to the applicant, additional PK data in adult and paediatric patients with PROS in the currently ongoing Phase II confirmatory study (referred to as **EPIK-P2**) will be provided.

The relevant pharmacokinetic (PK) properties of alpelisib were sufficiently characterized in the initial MAA and are summarized below as reflected in the adopted SmpC (section 5.2 PK properties). No PK revision of the SmpC is claimed, except the introduction of the possibility to administer the drug-product as an oral suspension in patients unable to swallow tablets. This point, together with addition of a new FCT 125 mg strength and dose selection in the paediatric patients are specifically discussed in the current report.

Absorption

Following oral administration of alpelisib, median time to reach peak plasma concentrations (Tmax) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen

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/Bioequivalence

Several oral formulations of alpelisib were developed and evaluated during the clinical development program for the Piqray® MAA where the commercial formulation consisted of film-coated tablets (FCT) at three strengths 50 mg (Light pink), 150 mg (Pale red) and 200 mg (Light red).

For the current submission, the commercial formulation of Alpelisib drug-product consisted of film coated tablets at three strengths, 50 mg (Light yellow), 125 mg (Dark yellow) and 200 mg (Pale yellow). The

colors have been adapted from the Piqray® FCTs for product differentiation purposes while retaining the same tablet core composition to maintain the consistent and reproducible manufacture of a high quality drug product. No relative BA study were performed between the FCTs of Piqray® and the proposed drug-product. Only in vitro dissolution tests were performed.

As part of Study **X2104**, a relative BA assessment was performed in patients to compare the biopharmaceutical performances of alpelisib administered orally as an entire tablet versus as a drinkable suspension (after crushing the tablet). Results of this study suggests similar systemic exposures on alpelisib between the two formulations (Test crushed tablet versus the reference whole tablet). The geometric mean Alpelisib AUClast and Cmax after single 300 mg dose of a crushed tablet administered as an oral suspension (Test, n=17 patients) were 23500 ng.hr/mL and 2200 ng/mL, respectively were slightly higher (21% and 19%, respectively) than those observed with the whole tablet (Reference, n=15 patients), 19400 ng.hr/mL and 1850 ng/mL, respectively. The same finding was observed after repeated doses. At steady state (D15), the geometric mean Alpelisib AUClast and Cmax for the oral suspension were 26300 ng.hr/mL and 2300 ng/mL, respectively, close to those for the tablet, 28600 ng.hr/mL and 2600 ng/mL, respectively.

Influence of food

Alpelisib absorption is affected by food. In healthy adult volunteers after a single 300 mg oral dose of alpelisib recommended in the oncology setting, compared to the fasted state, a high-fat high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased AUCinf by 73% and Cmax by 84%, and a LFLC meal (334 calories with 8.7 g of fat) increased AUCinf by 77% and Cmax by 145%. No significant difference was found for AUCinf between LFLC and HFHC with a geometric mean ratio of 0.978 (CI:0.876, 1.09), showing that neither fat content nor overall calorific intake has a considerable impact on absorption. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is the potential cause of the food effect. Hence, Alpelisib should be taken immediately after food at approximately same time each day.

Influence of gastric modifier

No dedicated study to investigate the effect on gastric modifier on alpelisib PK was performed as part of the initial submission (Piqray®), whereas Alpelisib is known to have a pH-dependent solubility.

Distribution

Alpelisib moderately binds to protein with a free fraction of 10.8% regardless of concentration. Alpelisib was equally distributed between red blood cells and plasma with a mean in vivo blood-to-plasma ratio of 1.03. As alpelisib is a substrate of human efflux transporters, penetration of the blood-brain barrier is not expected to occur in humans. The volume of distribution of alpelisib at steady state (Vss/F) is estimated at 114 litres (inter-subject CV% 49%).

Elimination

Alpelisib exhibits low clearance with 9.2 l/h (CV% 21%) based on population pharmacokinetic analysis based on data from adult healthy volunteers and cancer patients under fed conditions. The population-derived half-life, independent of dose and time, was 8 to 9 hours at steady state with 300 mg once daily recommended in the oncology setting.

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.

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.

Dose proportionality and time dependency

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

Steady-state plasma levels of alpelisib after daily dosing can be expected to be reached on day 3 following onset of therapy in most patients.

Pharmacokinetics in target population

No PK data were collected in PROS patients ≥ 2 years receiving Alpelisib as part of Study **EPIK-P1**. Thus, no new PK information for the claimed target population (adults and paediatrics) were generated in addition to those already known for the adult's breast cancer population.

No population PK analysis was performed for the PROS indication.

Special populations

Hepatic impairment

Based on a pharmacokinetic study in adult healthy volunteers and cancer patients with hepatic impairment, moderate and severe hepatic impairment had negligible effect on the exposure of alpelisib. The mean exposure for alpelisib was increased 1.26-fold in patients with severe (GMR: 1.00 for Cmax; 1.26 for AUClast/AUCinf) hepatic impairment.

Based on a Pop-PK in adult healthy volunteers and cancer patients that included 230 patients with normal hepatic function, 41 patients with mild hepatic impairment and no patients with moderate hepatic impairment, further supporting the findings from the dedicated hepatic impairment study, mild and moderate hepatic impairment had no effect on the exposure of Alpelisib.

Renal impairment

Based on a Pop-PK analysis in adult healthy volunteers and cancer patients that included 117 patients with normal renal function (eGFR ≥90 ml/min/1.73 m2) / (CLcr ≥90 ml/min), 108 patients with mild renal impairment (eGFR 60 to <90 ml/min/1.73 m2) / (CLcr 60 to <90 ml/min), and 45 patients with moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m2), mild and moderate renal impairment had no effect on the exposure of alpelisib.

Effect of age, weight and gender

The Pop-PK analysis based on data from adult healthy volunteers and cancer patients showed that there are no clinically relevant effects of age, body weight, or gender on the systemic exposure of alpelisib that would require alpelisib dose adjustment.

Race/Ethnicity

Pop-PK analyses based on data from adult healthy volunteers and cancer patients and pharmacokinetic analyses from a phase I study in Japanese adult cancer patients showed that there are no clinically relevant effects of ethnicity on the systemic exposure of alpelisib.

Elderly (age 65 years or above)

The pharmacokinetics of Alpelisib in adult patients ≥65 years of age have not been established.

Of 284 patients with HR-positive/HER2-negative advanced or metastatic breast cancer who received alpelisib in the phase III study (in the alpelisib plus fulvestrant arm), 117 patients were ≥65 years of age and 34 patients were between 75 and 87 years of age. No overall differences in exposure of alpelisib were observed between these patients and younger patients.

Paediatric population

No PK data were collected in this new claimed subgroup of patients from 2 to less than 18 years of age receiving alpelisib. In addition, no PK information was already available in the context of paediatric cancer population.

Overall, the PKs of alpelisib in paediatric patients <18 years is not considered elucidated yet.

Pharmacokinetic interaction studies

No data on drug interactions were generated in EPIK-P1.

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 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. For further details on the DDI profile of alpelisib see Clinical AR section 2.1.9 Pharmacokinetics interaction studies.

Of note, as a post-marketing measure (EMEA/H/C/004804/II/0012), a recent DDI study BYL719A2110 on the combination of alpelisib with rifampicin a strong inducer was assessed. The results demonstrated that a concurrent use of strong CYP3A4 inducers markedly reduced alpelisib exposure and thus may limit the clinical efficacy of alpelisib. Hence, the co-administration of strong CYP3A4 inducers with alpelisib should be avoided (see proposed SmPC).

3.3.1.2. Pharmacodynamics

3.3.2. Discussion on clinical pharmacology

Relative Bioavailability/Bioequivalence

A new FCT 125 mg strength is proposed to be commercialized. This strength have the same manufacturing process and qualitative composition and quantitatively proportional to the reference 50 and 200 mg strengths. In addition, the proposed strength is within the demonstrated PK linearity range from 30 mg to 450 mg. Overall, the claimed in vivo bioavailability study biowaiver could be acceptable from a PK perspective.

Drug administration

The relative bioavailabity of alpelisib after single and repeated QD administration of a film-coated tablet and a crushed film-coated tablet administered as an oral suspension in water was investigated in patients (Study X2104 Phase IB portion). The Applicant was asked to provide the statistical analyses on the primary PK endpoints in order to allow formal conclusions regarding the comparability of alpelisib bioavailability using both formulations In D121 response, the provided PK comparison of plasma PK exposures (Cmax, AUClast at Cycle 1 D1 and Cycle 1 D15 and AUCinf at D1) do not establish the similarity of biopharmaceutical performances (relative bioavailability) between the two formulations. This is plausibly explained by the lack of power of the comparison test (small sample size n= 15 for a parallel

group design). Therefore the claims related to relative bioavailability in section 5.2 could not be endorsed. Given the medical need for children patient unable to swallow, the uncertainty regarding the 50 mg dose determination and near complete bioavailability of alpelisib in the fed state, such statement could be maintained temporarily at this stage, provided the applicant a) commits to submit the results from the ongoing bioequivalence study CBYL719F12101 investigating the performance of the dedicated pediatric formulation (granules) with the available one (FCT), and b) update the SmPC accordingly with deleting the use of crushed FCT. **(OC)**.

The proposed paragraph "relative bioavailability" in section 5.2 and the possibility to administer the drug-product as an oral suspension in patients unable to swallow in section 4.2 should be deleted.

Pharmacokinetic in target population

No PK data in the target PROS population are provided in support of the current submission. The applicant claims that the current available PKs properties of alpelisib from the breast cancer submission is considered relevant for the new claimed population. Indeed, the primary metabolism pathway of alpelisib is amide hydrolysis, which is governed by multiple, ubiquitously expressed, high-capacity enzymes (esterases, amidases, and choline esterase). Thus, no significant impact of disease status (healthy volunteers, patients in the oncology setting or patients with PROS) on the PK of Alpelisib is expected. From the Rapporteur's point of view, there is no particular evidence against this hypothesis.

In the D21 response, the applicant committed, as requested, to provide reliable PK data of Alpelisib in both adult and paediatric patients with PROS planned in the ongoing Phase II confirmatory study EPIK-P2. The point is then considered solved.

Overall, no PK rationale is provided in support of the selected dosing regimens: 250 mg once daily (QD) for adults; 50 mg QD in paediatric patients [2-18 years] and the possibility of dose increase to 125 mg QD for paediatric patients ≥6 years old. These dosing regimens appears to be selected based only on the available clinical efficacy and safety during the initial compassionate use program; therefore, their evaluation must be done from a clinical perspective.

Co-Rapporteur's comments

The dose of 250 mg QD in PROS patients was selected based on the clinical/regulatory judgement during the initial compassionate use program. The preliminary efficacy and safety results observed in PROS patients led to initiate a program worldwide to evaluate alpelisib in adult patients with severe or life-threating complications of PROS. Despite differences in the dosing regimens between PROS patients and cancer patients have been highlighted, which would lead to a different exposure range among both indications, the specific benefit/risk ratio in PROS patients has determined the proposed dosing regimen. Indirectly, the different B/R ratio could be a consequence of differences in disease progression or patient's disease status, but this has not been confirmed.

Paediatrics / dose rationale

For the new claimed paediatric PROS population [2-18 years], no PK information was already available in the context of paediatric cancer population (in contrary to adults).

The MAH did not provide any PK simulation demonstrating the similarity in exposure between paediatric and adult patients and supporting the adequacy of the proposed 50 mg QD regimen (and subsequent dose escalation to 125 mg QD) in the paediatric population. This represents a significant limitation. Therefore, by considering the PopPK model (Report BYL719c-ppK-phase 3, previously developed in cancer population) and BW allometric scaling, the applicant was asked to derive the adequate dosing regimens across age groups in children that are expected to provide comparable exposures in adults; and to consequently discuss the relevance of the proposed dosing recommendations across age and body weight groups. In D121 response, the Applicant provided the information requested.

The results of the extrapolation analysis suggested that similar exposure to the adult population would be achieved when 125 mg or 8 mg/kg, 200 mg or 6.5 mg/kg, and 250 mg or 5 mg/kg is selected in pediatric PROS patients from 2-6, 6-12, and 12-18 years old, respectively. Based on the simulation analysis, the proposed regimen (50 mg QD) leads to an exposure in pediatric PROS patients that is 0.3-0.5-fold (depending on the age cohort) the predicted in adult PROS patients. As the Applicant pointed out, two critical assumptions have been considered: (1) Allometric scaling is suitable to describe the pediatric population, and (2) The statistical model (including covariates) of the SOLAR-1 population PK is suitable to describe PK in PROS disease conditions. It is agreed that the population PK model could be slightly different in terms of parameter estimation, but no differences are expected at the structural level, which could largely influence the exposure endpoints. In addition, based on the Applicant justification, no diseases differences are expected to impact on the PK properties between PROS and breast cancer patients. At the same time, no exposure-efficacy or exposure-safety profile in adult PROS patients has been presented that could inform of differences in the response profile. On the contrary, empirical use (case studies) of alpelisib in EPIK-P1 has been provided, informing that 74% patients did not change to the initial regimen (50 mg QD) and 17% increased to 100 or 150 mg QD. It would be relevant to know the age of those 6 patients when they had the dose increase (**OC**)

Overall, large uncertainties regarding the dose selection (50 mg QD) in pediatric PROS patients remain. The Applicant is conducting a clinical study EPIK-P2 with an arm of 125 mg QD, which will help to understand whether differences in the PK/PD relationship exist. So far, the dose level of 50 mg QD could be insufficient to achieve similar exposure to adult PROS patients and it could affect the overall efficacy.

Co-Rapporteur's comments

No experimental PK information in special sub-groups of patients with PROS has been provided. So far, no clinically relevant differences in exposure leading to different dosing recommendations have been established due to renal and hepatic impairment, extreme body weight, race, gender and age. However, as previously mentioned, no PK evidence was collected in the previous submission in paediatric patients (<18 years old). Moreover, the MAH did not provide any PK simulation demonstrating the similarity in exposure between paediatric and adult patients and supporting the adequacy of the proposed dosing regimen (and subsequent dose escalations) in the paediatric population. This represents a significant limitation that requires further clarification by the Applicant. Since the selection of the dosage regimen in paediatric patients cannot be established based on the available PK information, its evaluation must be based on the available efficacy and safety data.

The role of metabolic pathways is not fully clarified in paediatric patients with PROS due to the uncertainties regarding the exposure achieved in this subgroup of patients. Since no similarity in exposure has been demonstrated either *in silico* or *in vivo*, no similar DDI profile of alpelisib as victim or inducer can be assumed.

3.3.3. Conclusions on clinical pharmacology

No new PK information, in addition to those already known for adult cancer population, was collected in the claimed patients with PROS in support of the current submission. The applicant committed to provide a reliable PK characterization of alpelisib in both adult and paediatric patients with PROS in the ongoing Phase II confirmatory study EPIK-P2.

A number of concerns, particularly regarding rationale of dose selection, were posed to the applicant that were addressed. Overall, the selected dosing regimens in adult and paediatric patients lack any PK support and their evaluation must be based on the available clinical efficacy and safety data.

No major objections have been identified. However, the concern regarding relative bioavailability between the whole and crushed FCT formulations and the possibility to administer the drug-product as an oral suspension in patients unable to swallow tablets is still not endorsed and should be addressed (see PK LoQ).

3.3.4. Clinical efficacy

Table 1 Overview of the clinical development for alpelisib in the treatment of PROS:

Clinical Trial	Description	Status	Comments
CBYL719F12002 (EPIK-P1)	Retrospective chart review study evaluating the use of alpelisib for the treatment of patients with PROS through the ATU and the MAP	Completed Report available Aug-2021	Study Population: Paediatric and adult patients with severe or life-threatening PROS
CBYL719F12201 (EPIK-P2)	A Phase II, double blind study with an upfront, 16-week randomized, placebo controlled period, to assess the efficacy, safety and PK of alpelisib in paediatric and adult patients with PROS	Ongoing First Patient First Visit (FPFV): 19-Apr-2021	Study Population: Paediatric and adult patients with PROS (irrespective of disease severity). The study will have an overall follow-up of approximately 5 years to collect long-term safety and efficacy data in patients with PROS.
CBYL719F12401 (EPIK-P3)	A Phase II study to evaluate the long-term safety and efficacy of alpelisib in patients with PROS who previously participated in EPIK-P1	Ongoing FPFV: 27-Jan-2022	Study Population: Patients previously enrolled in EPIK-P1. The patients will have data collected for approximately 2 years in the retrospective period, and will be followed up for at least 5 years in the prospective period or until discontinuation of treatment.
CBYL719F12101	A single-centre, randomized, open label, three-period crossover study to investigate the bioequivalence of the alpelisib granule and the FCT formulation, and the effect of food on the alpelisib granule formulation in adult healthy volunteers	Ongoing FPFV: 03-Feb-2022	Study Population: Adult healthy volunteers

PROS: PIK3CA-Related Overgrowth Spectrum – ATU : Temporary Authorisation for Use – MAP : Managed Access Program - FPFV : First patient first visit

3.3.4.1. Dose-response studies

No formal dose finding study was conducted, the dosage regimen used during the ATU 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).

No paediatric PK data are available at the time this application is made. Results of the double blind phase II study, 16-week randomized, placebo controlled period, that aim to assess the efficacy, safety and PK of alpelisib in paediatric and adult patients with PROS (EPIK-P2) are expected in 2024.

3.3.4.2. Main study

CBYL719F12002 (EPIK-P1)

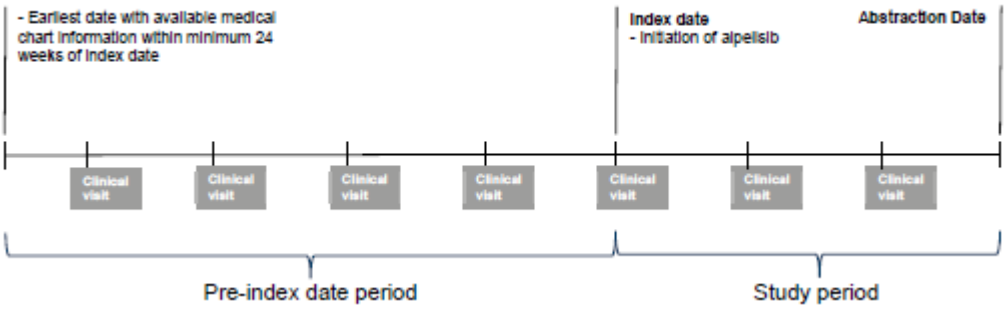
Methods

This study (CBYL719F12002; EPIK-P1) is a site-based retrospective non-interventional medical chart review of patients 2 years of age and older with severe or life-threatening PROS who have received alpelisib as part of a compassionate use program (i.e. patients were treated under the ATU in France or the MAP outside of France).

This study abstracted data from all eligible patients 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.

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).

Figure 4 Study design:



Study Participants

<u>Inclusion/exclusion criteria EPIK P1:</u>

Patients included in this study met all of the following **inclusion criteria**:

- Patient (adult or paediatric) is ≥2 years of age *
- Patient has a physician confirmed/documented diagnosis of PROS*
- Patient has a documented evidence of a mutation in the PIK3CA gene*

- Patient's condition was assessed by the treating physician as severe or life threatening and treatment was deemed necessary*
- Patient has been treated with at least one dose of alpelisib, initiated at least 24 weeks before the abstraction date
- Patient has medical chart history available during enrolment in the Novartis MAP

** Inclusion criteria for MAP enrolment (assessed at the time of alpelisib initiation).*

Exclusion criteria EPIK P1: none

Main inclusion/ exclusion criteria for the provision of Managed Access Program (initial Feb 2018):

Inclusion criteria

- An independent request should be received from the Treating Physician (in some instances from Health Authorities, Institutions or Governments);
- The patient to be treated has a serious or life threatening disease or condition, and no comparable or satisfactory alternative therapy is available to monitor or treat the disease or condition;
- There is a potential patient benefit to justify the potential risk of the treatment use, and the potential risk is not unreasonable in the context of the disease or condition to be treated;
- Patients eligible for inclusion in this Treatment Plan have to meet all of the following criteria:
- Adult or paediatric patients ≥2 years of age, with a confirmed diagnosis of PROS and documented evidence of a mutation in the PIK3CA gene, as determined by a local laboratory.
- The treating physician has determined that the patient's condition is severe or life threatening, treatment is necessary and there are no other feasible alternatives for the patient.

Exclusion criteria

- Patient has history of hypersensitivity to any drugs or metabolites of PI3K inhibitor or any of the excipients of alpelisib.
- Patient with uncontrolled diabetes mellitus (Type I or II).
- Patient who has other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate administration of alpelisib (e.g. Active or uncontrolled severe infection, chronic active hepatitis, immune-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)
- Patient has a known history of Steven Johnson's syndrome or toxic epidermal necrolysis.
- Patient who does not apply highly effective contraception during the treatment with alpelisib and through the duration as defined below after the final dose of alpelisib
- Patient is pregnant or lactating.

New exclusion criteria for the provision of Managed Access Program (Version 1.0 Fev 2020):

- Patient with uncontrolled diabetes mellitus type I or not controlled type II (based on FPG and HbA1c)
- Patient who has other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate administration of alpelisib (e.g. Active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)
- Patient has a known history of severe cutaneous reactions like Steven Johnson's syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- History of pancreatitis within 1 year of screening or past medical history of chronic pancreatitis
- Subject with Child Pugh score B or C
- Subjects with unresolved osteonecrosis of the jaw
- Subject is currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment:
    - Strong inducers of CYP3A4
    - Inhibitors of BCRP
- Patient who is concurrently being treated with drugs known to be strong inhibitors or inducers of the isoenzyme CYP3A; switching to different medications prior to start of program treatment is allowed within the last 5 days prior to starting program treatment
- Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to start of program treatment, or who have not fully recovered from side effects of such treatment.

Treatments

The compassionate use program recommendation for alpelisib was 50 mg daily, taken with food in paediatric patients (2 to 17 years), and 250 mg daily, taken with food in adult patients (≥ 18 years).

In the Treatment Plan for the ATU in France version 1 (Feb 2018) dosing recommendations were:

4.1. Posology and method of administration

Posology

There is no safety and efficacy data available besides from the current clinical developments of alpelisib in oncology. The posology will be determined by the prescriber based on the patient's needs.

Adults

The safety and the efficacy of alpelisib are currently being evaluated in clinical trials in oncology.
The recommended initial dose in adult patients treated for a breast cancer is 300 mg alpelisib once daily in a Phase III study.

Children

There is only very limited data available on the safety and efficacy of alpelisib in children under the age of 18.

In the absence of toxicological studies in juvenile animals, there is a need for increased monitoring of the growth and puberty in children into adolescence.

Duration of treatment

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs [

Dose modifications

During oncology clinical studies in adult patients, in case of severe or intolerable toxicity suspected to be related to alpelisib, alpelisib should be interrupted with resumption at a same or reduced dose level, or permanently discontinued. In the oncology studies, dose reductions below 200 mg were not used and alpelisib was discontinued instead

Missed doses

If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken on the next day at the usual time.

Specific populations

Renal impairment

The safety and efficacy in patients with renal impairment has not been established.

Hepatic impairment

The efficacy and safety of alpelisib in patients with hepatic impairment has not been established.

Elderly patients

The efficacy and safety of alpelisib in elderly patients have not been established.

Method of administration

Alpelisib is for oral use. Alpelisib should be taken orally once daily at the same time every day, preferably in the morning, within 1 hour after a meal or snack.

Alpelisib tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing).

Tablets that are broken, cracked, or otherwise not intact should not be ingested.

In the global Managed Access program, treatment Plan initial version (2018) dosing recommendations were:

In **Adult** patients, alpelisib was administered at a starting dose of 250 mg orally once daily on a continuous dosing schedule and 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; no dose reductions were allowed.

The following general guidelines must be followed for alpelisib administration:

- Patients (or responsible parent or guardian in case of paediatric patients <18 years age, [paediatric age dependent on country regulations]) should be instructed to take the dose of alpelisib once daily at approximately the same time **each day within 1 hour after a meal** (preferably in the morning after breakfast).
- If, for any reason, a breakfast (or other meal) is not consumed, then the patient should take the treatment with a glass of water within 1 hour after a snack at any later point in time.

- Alpelisib should be taken with a glass of water. Patients should swallow the tablets as a whole and not chew them. In patients with swallowing dysfunction (including paediatric patients who are unable to swallow), alpelisib film-coated tablets can be administered as drinkable suspension by crushing the tablets under water with a spoon.

In the Managed Access Program, treatment Plan version 1 (Feb 2020) dosing recommendations were:

In **Adult** patients, alpelisib were administered at a maximum starting dose of 250 mg orally once daily on a continuous dosing schedule and could be adjusted for toxicity.

In **Paediatric** patients, alpelisib were administered at a maximum starting dose of 50 mg orally once daily on a continuous dosing schedule and can be interrupted for toxicity; no dose reductions were allowed.

The following general guidelines must be followed for alpelisib administration:

Alpelisib should be taken **immediately after food**, at approximately the same time each day. The maximum recommended daily dose of alpelisib was 300 mg.

Dose modifications

For patients who did not tolerate the dosing schedule specified in the Treatment Plan, dose adjustments were permitted in order to allow the patient to continue treatment through MAP.

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 should permanently discontinue treatment. Guidelines for the suggested management of selected toxicities are described below.

Table 2 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

Objectives

Primary objective

- efficacy of alpelisib as measured by the proportion of patients with response at Week 24 (± 4 weeks).

Secondary objectives were to assess:

- 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
- type of 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.

Outcomes/endpoints

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.

Independent central radiology review (ICRR)

The target lesions were independently selected by ICRR using the pre-index date scans and clinical information regarding clinical/functional impact provided by the treating physician. PROS-lesion radiographic response and non-response were defined based on PROS-related lesion volume reduction.

Up to three PROS-related target lesions were chosen for measurement over the course of the study. PROS-related lesion volume was defined as the sum of the volume of the individual target lesions and was measured at each MRI (or other imaging modality) assessment during the study.

Note: photographs were presented to the readers to supplement the assessment of the target lesions, but were not used for measurement purposes.

In addition to the above, the target lesion(s) was required to be:

- Anatomically reproducibly defined tissue(s) masses, composed of one or several tissue types
- Accurately measurable by imaging technique, MRI, or other imaging modality
- Identified at the index date and ideally its size would be at least 2 cm in longest diameter at the index date (for each selected lesion).

Secondary endpoint

Changes in the sum of measurable target lesion volume (1 to 3 lesions) over time

> Percent change in the sum of measurable target lesion volume (1 to 3 lesions), assessed by an ICRR of imaging scans, as measured by the change between the index date (or up to 24 weeks prior) and key time-points following the index date.

Changes in the sum of all measurable (target and non-target) lesion volume over time

> Percent change in the sum of all measurable (target and non-target) lesion volume, as assessed by an ICRR of imaging scans, as measured by the change between the index date (or up to 24 weeks prior) and key time-points following the index date.

Changes in the sum of all measurable non-target lesion volume over time

> Percent change in the sum of all measurable non-target lesion volume, as assessed by an ICRR of imaging scans, as measured by the change between the index date (or up to 24 weeks prior) and key time-points following the index date.

Duration of response (DOR)

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.

Description in type of medication and non-drug therapies over time

PROS-related treatment(s) other than alpelisib

Medication(s) (e.g. concomitant medications for the management of PROS-related complications and 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).

PROS-related surgeries (e.g. debulking or vascular surgery as well as the intended site of the procedure).

Alpelisib treatment (e.g. dose, dose adjustments, duration of treatment, dose interruptions, discontinuation, exposure, and dose intensity).

Changes in PROS symptoms and complications over time were presented eg. Life-threatening complications (e.g. stroke, pulmonary embolism), pain, and fatigue.

Changes in functional status

Work/school/pre-school attendance

Mobility

Performance status (e.g. ECOG (Eastern Cooperative Oncology Group), Lansky and Karnofsky score)

Changes in HRU

Non-medical resource use (e.g. physical therapy, occupational therapy, home care services)

Hospitalizations (including relevant medical interventions undertaken if related to PROS)

Emergency room visits (including relevant medical interventions undertaken if related to PROS)

Changes in clinical and laboratory assessments

Cardiac assessments (e.g. electrocardiogram (ECG), BNP)

Laboratory assessments (e.g. D-dimer, fibrinogen, haemoglobin, renal function, albumin, protein)

Vital signs (e.g. height, weight, blood pressure, resting pulse)

Growth and development

Safety and tolerability of alpelisib

Sample size

This study aimed to report efficacy and safety of eligible patients at participating sites who were treated with alpelisib by collecting the medical chart information. As a result, no formal sample size calculation was performed.

Based on the feasibility assessment conducted at each MAP site that expressed interest in participating in this study in May 2019, approximately 65 patients satisfied the study inclusion criteria. Assuming that

between 15% and 20% of patients would not accept participation in the study, 50 patients were considered for the estimation.

Randomisation and blinding (masking)

This study is a retrospective chart review of patients who have received alpelisib as part of a compassionate use program. Thus no randomisation or blinding were applied.

Statistical methods

The primary and secondary analyses for this study were descriptive in nature (estimation based), and therefore, no hypothesis testing will be conducted. The data abstracted in this study were summarized as described below. Descriptive analyses were conducted where continuous data were summarized by measures that may include the mean, SD, median, IQR, minimum, and maximum. Categorical and binary data were presented by frequency counts and percentages. All descriptive analyses were presented along with their 95% CIs as appropriate.

The data sources and measurement for this study were retrospectively abstracted from medical charts of eligible patients with PROS at participating clinical sites. Physician narratives were also generated based on information recorded in the patients' medical charts and reported in the eCRF. This information was used to write the physician narratives. An eCRF completion guide was developed and training related to data entry was completed for each site personnel.

Data abstraction and management: At the participating sites, the data from eligible patients were retrospectively abstracted from charts and pooled longitudinal information to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS. The data also included imaging scans (i.e., MRI scans, CT scans), clinical photographs, as available. The data were sent to an ICRR for evaluation of response and were used for the study endpoints. The physician evaluation was based on the clinical impact of the lesion he/she had selected at the start of the treatment.

The applicant generated physician narratives based on information recorded in the patients' medical charts and reported in the eCRF. For these narratives, each physician was asked to review the data qualitatively and provide his/her personal assessment of the clinical outcome of the treatment with alpelisib for each individual patient.

A data management process was pre-specified in a DMP document. The applicant assured that database quality processes were followed including review of the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the DMP.

Physician assessment: In the medical record, it was anticipated that some lesions were already identified by the treating physician based on the clinical/functional impact of such lesions on the patient and were assessed over time. The clinical/functional impact was associated with at least one of the following: patient's complaints, clinical symptoms, impaired organ function, and/or functional limitations affecting patient's everyday life. To mitigate potential physician bias in assessing PROS lesions response to treatment and to ensure a homogenous assessment of response across patients, sites and countries, the target lesions for the analysis of study endpoints were independently selected via ICRR using the pre-index date scans and clinical information regarding symptoms related to lesions as provided by the treating physicians. Subsequently, response was assessed via ICRR following review criteria specified in a charter which was developed prior to the review of the patients scans. Furthermore, all available MRI scans and CT scans up to the cut-off date were submitted for assessment by ICRR. Lastly, up to three PROS-related target lesions were chosen for measurement over the course of the study.

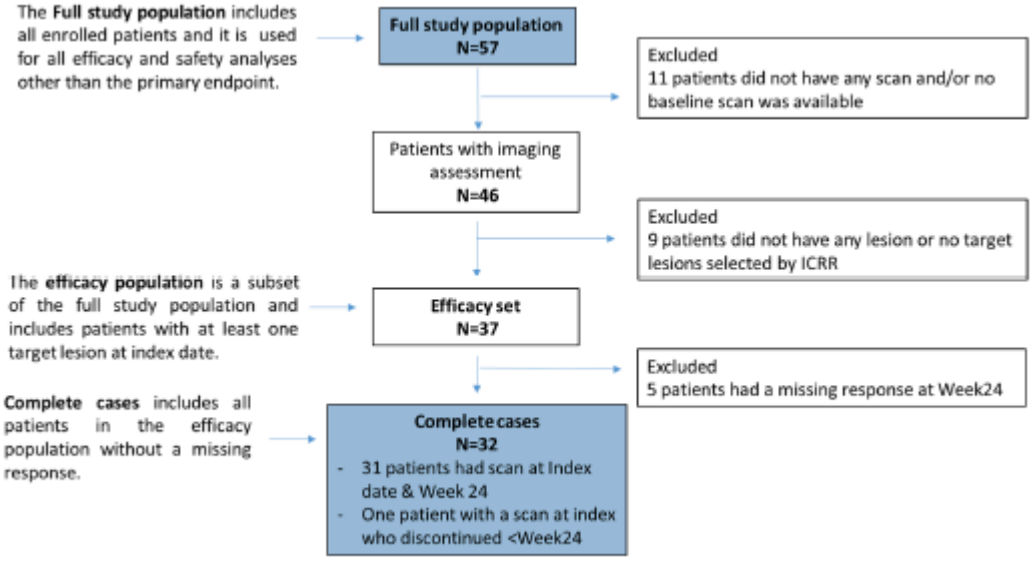
Results

Participant flow

Overall, of the 58 patients included in the study, 57 patients were in the Full study population, as one patient withdrew consent.

The details of patients included in each of the analysis populations is depicted in Figure 5

Figure 5 Study population



Patient disposition

Overall population:

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%).

Median duration

In the overall population, the median duration between the index date and end of study was 18.1 months (range: 4.4 to 49.9 months), corresponding approximately to 79 weeks.

In paediatric patients, the median duration between the index date and end of study was 17.97 months (range: 4.4 to 41.8 months), corresponding approximately to 78 weeks.

In adult patients, the median duration between the index date and end of study was 19.17 months (range: 8.0 to 49.9 months), corresponding approximately 83 weeks.

Table 3 Patient disposition by age category (Full study population)

Disposition Reason	Pediatric patients				Adult patients	All patients
	2-5 years N=11 n (%)	6-11 years N=12 n (%)	12-17 years N=16 n (%)	< 18 years N=39 n (%)	≥ 18 years N=18 n (%)	N=57 n (%)
Patients treated	11 (100)	12 (100)	16 (100)	39 (100)	18 (100)	57 (100)
Treatment ongoing	11 (100)	11 (91.7)	14 (87.5)	36 (92.3)	16 (88.9)	52 (91.2)
Discontinued	0	1 (8.3)	2 (12.5)	3 (7.7)	2 (11.1)	5 (8.8)
Reason for discontinuation						
Subject decision	0	0	1 (6.3)	1 (2.6)	2 (11.1)	3 (5.3)
Physician decision	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Other	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
No efficiency	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. Treatment ongoing at the time of data cut-off.
Source: Table 14.1-1.2

Recruitment

Start of data collection 09-Jun-2020

End of data collection (Last date of data collection) 16-Apr-2021

Final report of study results 23-Aug-2021

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)). Forty-four of the total 57 patients (77.2%) were included at the Necker Hospital, Paris, France.

Per protocol amendment, the cut-off date definition was changed to avoid missing data due to the COVID-19 pandemic. The cut-off date for the study to a fixed date of 09-Mar-2020.

Conduct of the study

Amendment 01 (04-May-2020)

No patients were included prior to Protocol Amendment 01.

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. This approach allowed Novartis to minimize the impact of the SARS-CoV-2 (COVID-19) pandemic on the study integrity.

Specifically, the cut-off date definition was changed to avoid missing data due to the COVID-19 pandemic. In the original protocol, the cut-off date was defined as the date of the start of data entry (the data abstraction date). This amendment changed the cut-off date for the study to a fixed date of 09-Mar-2020. 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.

Following discussion with FDA in the context of Type B meeting on 02-Apr-2020, the primary analysis was modified at the Agency's request. 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 performed as a sensitivity analysis (instead of as the primary analysis).

Duration of response (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.

The primary endpoint was also summarized and reported by sex.

Baseline data

Demographic data

The median age of all patients was 14 years (range: 2 to 50 years). Most of the patients were female (33 patients, 57.9%). Race and ethnicity were not reported for the majority of patients (50 patients, 87.7%) as this was not permitted by the regulations in France. The median BMI was 20.19 kg/m2 (range: 13.4 to 34.8 kg/m2). The performance status scores were evaluated for 47 patients (82.5%) and 30 patients had a Lansky and Karnofsky score ≤ 70 at the index date.

Table 4 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	Pediatric 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)						
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: Table 14.1-3.1

Disease history

Overall population:

Overall, patients had heterogeneous manifestations of PROS. The subtype 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). The majority of patients 53 patients (93.0%) has their disease diagnosed at birth. Only four patients (7.0%) had early childhood-onset of their overgrowth. A mosaic distribution was evident in all except one patient (Table 5).

Table 5 PROS disease history at the index date by age category (Full study population)

Disease history	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (≥18 years) 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: Table 14.1-3.2

Mutation status

All patients were tested for PIK3CA mutations at a local laboratory, mostly by NGS.

PIK3CA mutation subgroups were categorized as "Frequent" and "Less frequent" based on literature search on different mutation prevalence in PROS patients. "Frequent mutations" were identified by using the cut off of 2%.

Below the list of mutations under "Frequent" and "Less frequent" categories:

- "Frequent" included H1047R, E542K, H1047L, E545K, E453K and C420R.

- "Less frequent" included E726K, H1047Y, E110del, C378Y, E545A, M1043V, E81K, I391M, Q546K, M1043I, P104L, Q546H, G914R, G118D, N345K, E418K, Q546R,nN1044K, E365K, H554Tfs*6, F909L, T1025A, A1035V, G1049R, G1050S, Y56*, R88Q, G106_R108>I, G106R, G106V, K111del, N114S, R115P, V344M, V344G, V346L, V346_N347insK, D350G, G364R, C378R, P449T, H450R, P471L, D538N, P539S, E542G, E542V, I543V, E545D, E545G, 53Tfs*20, E600K, C901F, G914A, S1008F, Y1021H, Y1021C, T1025N, A1035T, M1040I, A1046V, H1047Q, H1048R, G1049S, N1068Kfs*5 and other.

Numbers analysed

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.

Table 6 Full study population over time (Full study population)

Time-point	Number of patients (N)
Index date	57
4 weeks	57
12 weeks	57
24 weeks	56
36 weeks	54
52 weeks	52
63 weeks	44
74 weeks	38
85 weeks	28
96 weeks	20
107 weeks	19
118 weeks	19
129 weeks	19
140 weeks	19
151 weeks	18
162 weeks	9
173 weeks	2
184 weeks	2
195 weeks	1
206 weeks	1
217 weeks	1

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
The Full study population includes all patients who satisfy the study inclusion criteria.
Source: Table 14.1-2.1

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.

Table 7 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: Table 14.1-2.3

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.

Outcomes and estimation

Primary efficacy analysis

Overall population:

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). The proportion of patients with response at Week 24 or 6 months (± 4 weeks) was 37.5% (12/32 patients) with 95% CI: 21.1; 56.3 based on ICRR.

Table 8 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.

- Patients were 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.
Source: Table 14.2-2.1

Non-responders

Of the 20 non-responders from the complete case analysis, none had a progressive disease (PD) at Week 24, 19 patients had non-response-non-PD and one patient was defined as non-responder as the patient permanently discontinued alpelisib prior to Week 24 (no efficiency as per patient decision). None of the patients required surgery as rescue therapy (due to disease progression) between the index date and Week 24.

Table 9 Summary of non-responses at Week 24 with complete cases (Efficacy population)

	All patients N=20 n (%)
Non response – PD	0
Non response - Non PD	19 (95.0)
Patient permanently discontinued alpelisib prior to 24 weeks of treatment	1 (5.0)
Patient required surgery as rescue therapy between index date and Week 24	0
Patients with MRI scan performed at Week 24 for which the volumetric measurement cannot be calculated	0

A patient may have multiple criteria. Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis. Non-PD is when at least one criteria for PD is not met. Target and non-target lesions are intended as "measurable" where not otherwise specified. Patients with MRI scan performed at Week 24 for which the volumetric measurement cannot be calculated is intended or when no scan is available/readable for any of the lesions identified at baseline. Week 24 window (± 4 weeks) is intended as Week 24 or 6 months after index date, where 6 months is approximated to Week 27.

Source: Table 14.2-2.2

Subgroup 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 subtype. Of the 23 patients with frequent mutation type 12 patients (52.2%) were responders. Response rate was higher in the adult population (5/9 patients, 55.6%) than in the paediatric population (7/23 patients, 30.4%).

Table 10 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.

Source: Table 14.2-2.3

Secondary efficacy analyses

Changes in the sum of measurable target lesion volume

Overall, 31 patients had an imaging assessment at the index date and at Week 24. In total 23/31 patients (74.2%) had any reduction in the sum of target lesion volume.

The mean (SD) percentage change from the index date at Week 24, in the sum of target lesion volume (1 to 3 lesions), as assessed by ICRR was -13.66% (18.921).

Paediatric population:

Twenty two patients had an imaging assessment at the index date and at Week 24. In total 15/22 patients (68.2%) had any reduction in the sum of their target lesion volume.

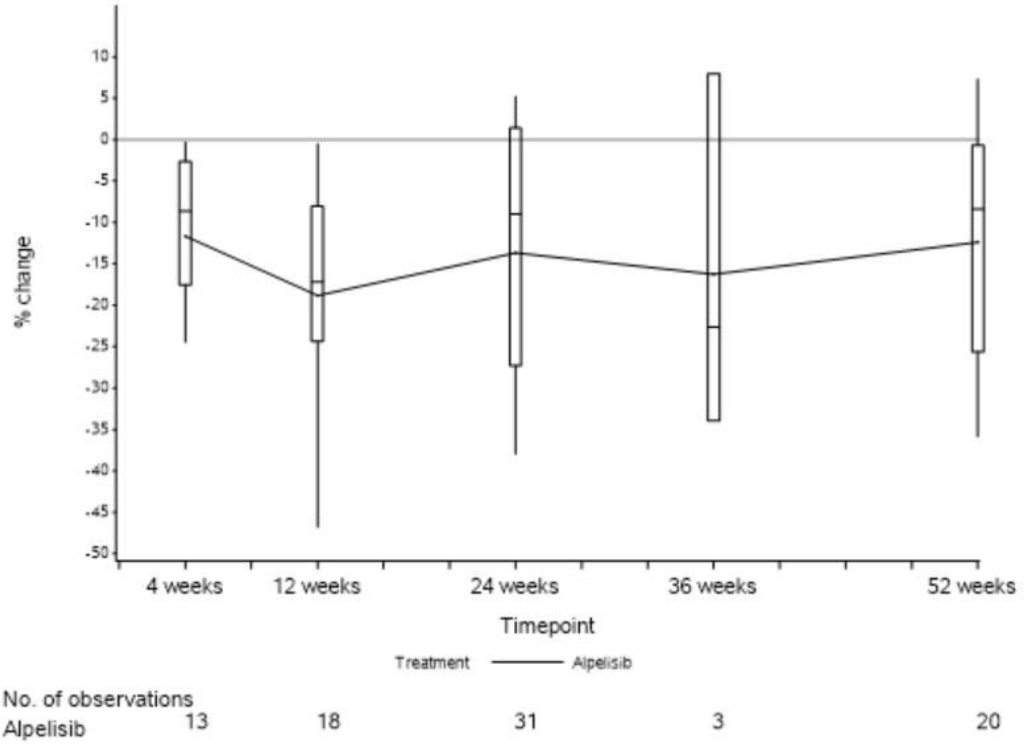
The mean percentage change from the index date at Week 24, in the sum of target lesion volume (1 to 3 lesions), as assessed by ICRR was -11.20%.

Adult population:

All nine patients had an imaging assessment at the index date and at Week 24. In total 8/9 patients (88.8%) had any reduction in the sum of target lesion volume.

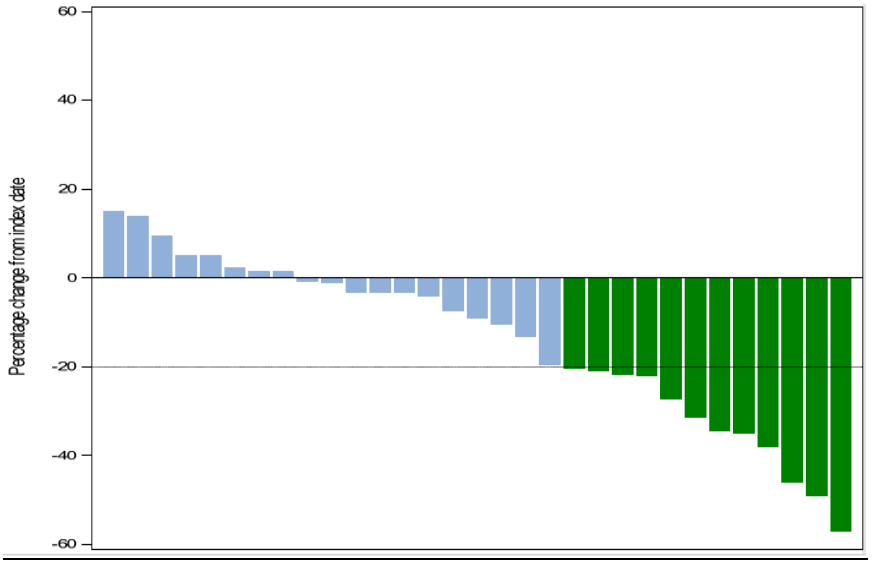
The mean percentage change from index date at Week 24, in the sum of target lesion volume (1 to 3 lesions), as assessed by ICRR was -19.69%.

Figure 6 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

Figure 7 Individual percentage change in sum of target lesion volume at Week 24 (Efficacy population; All patients)



Patients who are responders for the primary endpoint are highlighted in green. Non-responders are highlighted in blue. Only patients with a value at both index date and Week 24 are included in the calculation of change
Source: [PROS SCE Appendix 2-Figure 3.1-1.5]

Changes in the sum of all measurable (target and non-target) lesion volume

As no measurable non-target lesions were identified, the results for changes in the sum of all measurable (target and non-target) lesion volume were identical to the results presented above.

Duration of response

Among the 12 patients with a response, the median DOR was not estimable as no events (progression or death) were 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) with two patients censored on Day 1 as they did not have any further imaging assessment after Week 24. Seven patients had time to censoring >6 months and six patients >12 months.

Table 11 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

Over time, PROS-related medication 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. 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.

Table 12 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

Pain medications

The numbers of patients receiving pain medication (including opioids) slightly decreased 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%).

PROS-related non-drug treatments and other medical interventions

During the Full study period, 48 patients (84.2%) had received at least one PROS-related non-drug treatments and other medical interventions.

Types of supportive non-drug treatments received by ≥ 5% of the patients were compression garments (23 patients, 40.4%); supportive mobility devices excluding wheelchair (10 patients,17.5%); wheel chair (9 patients, 15.8%); blood transfusion (3 patients, 5.3%); and sclerotherapy (3 patients, 5.3%). Of note, of the 9 patients requiring wheel chair assistance (due to the imputation rules applied; missing or partial start and end dates) 4 patients had improvement and stopped using wheel-chair under alpelisib treatment.

PROS-related surgery

After the initiation of alpelisib treatment and until end of the study, two patients had surgeries due to disease progression.

Table 13 PROS-related completed surgeries during the study period by age category (Full study population)

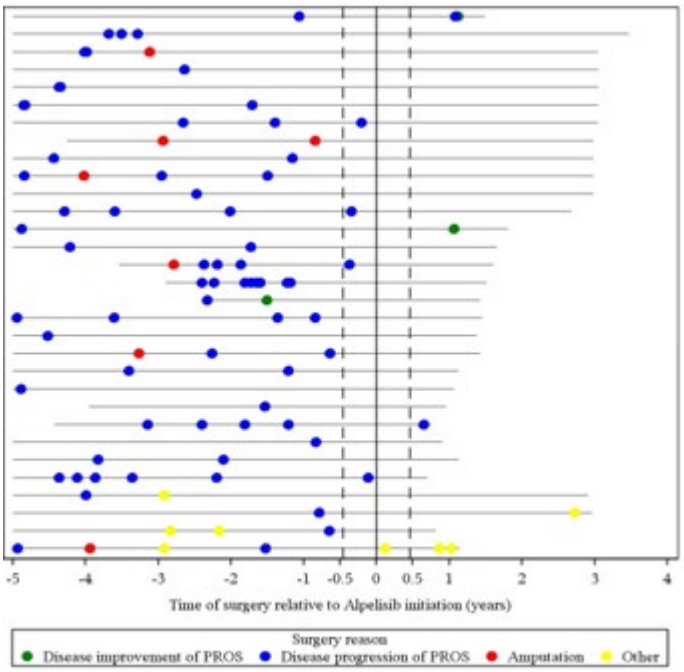
Characteristic	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (≥18 years) N=18	All patients N=57
Number of patients with at least one surgery-n (%)	0	1 (8.3)	4 (25.0)	5 (12.8)	2 (11.1)	7 (12.3)
Number of surgeries per patient						
N		1	7	8	3	11
Mean (SD)		1.0 (NA)	1.8 (0.96)	1.6 (0.89)	1.5 (0.71)	1.6 (0.79)
Median		1.0	1.5	1.0	1.5	1.0
Q1-Q3		1.0-1.0	1.0-2.5	1.0-2.0	1.0-2.0	1.0-2.0
Min-Max		1-1	1-3	1-3	1-2	1-3
Number of surgeries per patients in categories-n (%)						
0	11 (100)	11 (91.7)	12 (75.0)	34 (87.2)	16 (88.9)	50 (87.7)
1	0	1 (8.3)	2 (12.5)	3 (7.7)	1 (5.6)	4 (7.0)
2	0	0	1 (6.3)	1 (2.6)	1 (5.6)	2 (3.5)
>2	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Time from index date to first surgery (months)						
≤ 6 months	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
6 - ≤ 12 months	0	1 (8.3)	0	1 (2.6)	1 (5.6)	2 (3.5)
12 - ≤ 24 months	0	0	2 (12.5)	2 (5.1)	1 (5.6)	3 (5.3)
24 - ≤ 36 months	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
36 - ≤ 52 months	0	0	0	0	0	0
> 52 months	0	0	0	0	0	0
Type of surgery[1]-n (%)						
Other	0	1 (50.0)	1 (14.3)	2 (22.2)	1 (33.3)	3 (25.0)
Scoliosis	0	0	3 (42.9)	3 (33.3)	0	3 (25.0)
Cosmetic	0	0	1 (14.3)	1 (11.1)	1 (33.3)	2 (16.7)
Debulking	0	1 (50.0)	1 (14.3)	2 (22.2)	0	2 (16.7)
Functional	0	0	1 (14.3)	1 (11.1)	1 (33.3)	2 (16.7)
Site of surgery[1]-n (%)						
Thorax	0	0	3 (42.9)	3 (33.3)	1 (33.3)	4 (33.3)
Head	0	1 (50.0)	1 (14.3)	2 (22.2)	0	2 (16.7)
Other	0	1 (50.0)	1 (14.3)	2 (22.2)	0	2 (16.7)
Abdominal region	0	0	0	0	1 (33.3)	1 (8.3)
Bone	0	0	1 (14.3)	1 (11.1)	0	1 (8.3)
Limb	0	0	1 (14.3)	1 (11.1)	0	1 (8.3)
Skin	0	0	0	0	1 (33.3)	1 (8.3)
Reason for surgery[1]-n (%)						
Other	0	0	4 (57.1)	4 (44.4)	2 (66.7)	6 (50.0)
Disease improvement	0	0	2 (28.6)	2 (22.2)	1 (33.3)	3 (25.0)
Disease progression	0	2 (100)	1 (14.3)	3 (33.3)	0	3 (25.0)

Surgery is counted only once if on the same day the patient has had different type of procedures and/or same procedure on a different site.
[1]A patient may have multiple sites of surgery and types of surgery on the same day.
Total number of surgeries is used as denominator.

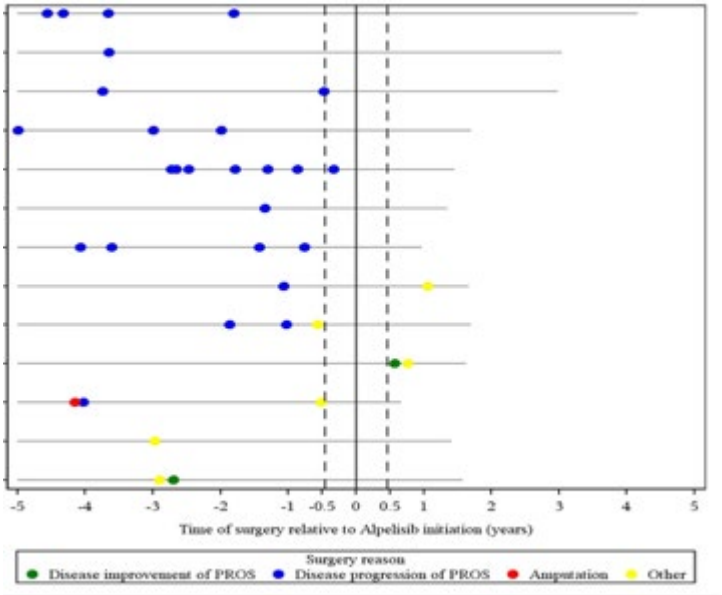
Time from index date to first surgery (months) = (first surgery after index date) – (index date) +1 / 30.4375.
Surgery performed on or after the start of study treatment are summarized.
Source: Table 14.3-2.8

Figure 8 Incidence of PROS-related completed surgeries from 5 years prior to alpelisib initiation to end of study by age (Full study population)

Paediatric (<18years)



Adults (≥ 18 years)



The dots represent an occurrence of surgery. A red dot indicates a surgery for an amputation, while a blue dot indicates a surgery due to disease progression of PROS. The green dot indicates surgery due to disease

improvement, surgery for which the patients were previously not eligible based on their medical conditions but who became eligible later when experiencing clinical improvement from alpelisib treatment.
Completed surgeries are reported. The x-axis represents the period from 5 years prior to alpelisib treatment start until the end of the study. The vertical solid line at time 0 on the x-axis represents the start date of alpelisib treatment. Vertical dotted lines refer to -24 weeks and +24 weeks from the index date. Source: [PROS SCE Appendix 1-Figure 3.1-1.13]

Changes in PROS symptoms and complications

Improvement in PROS symptoms and complications was defined based on at least one grade reduction or resolution of the event, considering the Full study population (Table 14).

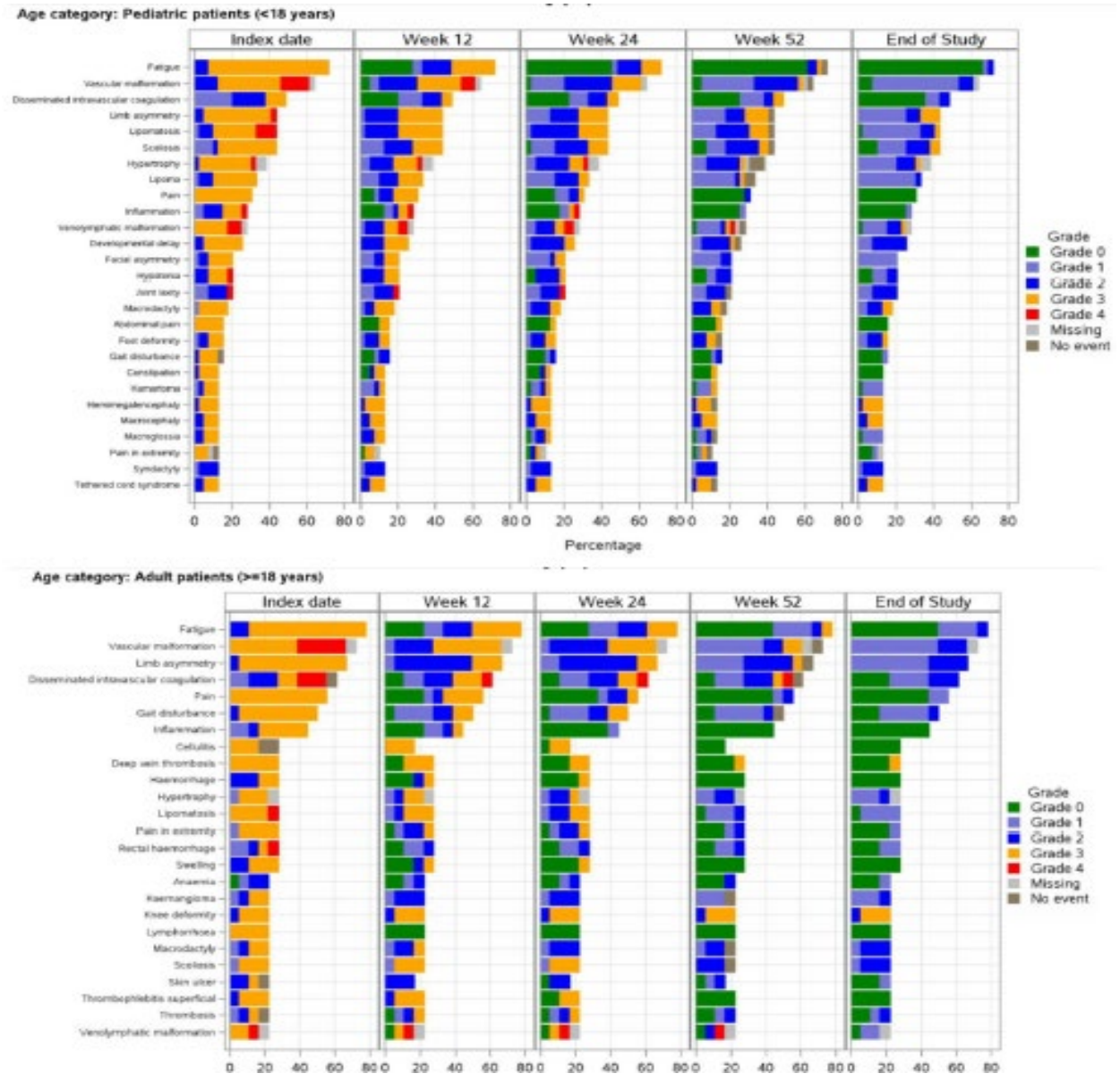
In the overall population, the most frequently reported PROS-related signs and symptoms at the index date were fatigue (73.7%), vascular malformation (66.7%), limb asymmetry (50.9%), disseminated intravascular coagulation (50.9%) and pain (38.6%).

Table 14 Most frequent PROS-related signs and symptoms during the first 24 weeks (Full study population)

	Paediatric patients (< 18 years) N=39		Adult patients (≥ 18 years) N= 18		All patients N= 57	
PROS-related signs or symptoms	**Index**	**Improved[1] by Week 24**	**Index**	**Improved[1] by Week 24**	**Index**	**Improved[1] by Week 24**
Fatigue	28 (71.8)	22 (78.6)	14 (77.8)	10 (71.4)	42 (73.7)	32 (76.2)
Vascular malformation	25 (64.1)	20 (80.0)	13 (72.2)	10 (76.9)	38 (66.7)	30 (78.9)
Disseminated intravascular coagulation	19 (48.7)	11 (57.9)	10 (55.6)	5 (50.0)	29 (50.9)	16 (55.2)
Limb asymmetry	17 (43.6)	11 (64.7)	12 (66.7)	9 (75.0)	29 (50.9)	20 (69.0)
Pain	12 (30.8)	11 (91.7)	10 (55.6)	9 (90.0)	22 (38.6)	20 (90.9)

[1]Improvement is defined based on CTC grade reduction or resolution of the event. % are calculated on the number of patients reporting the event at the index date. Source: [PROS EPIK-P1-Table 14.3-2.5]

Figure 9 Shift in CTC grade from index date to key post-index visits of the most frequent PROS-related signs and symptoms by age category (Full study population)



Pain (composite endpoint)

A questionnaire recording pain severity (i.e. Wong Baker, FLACC and Numerical scale rating) was collected for 11/57 patients (six paediatric and five adult patients).

Six patients had reported data at both the index date and Week 24, all of them remained stable with no pain.

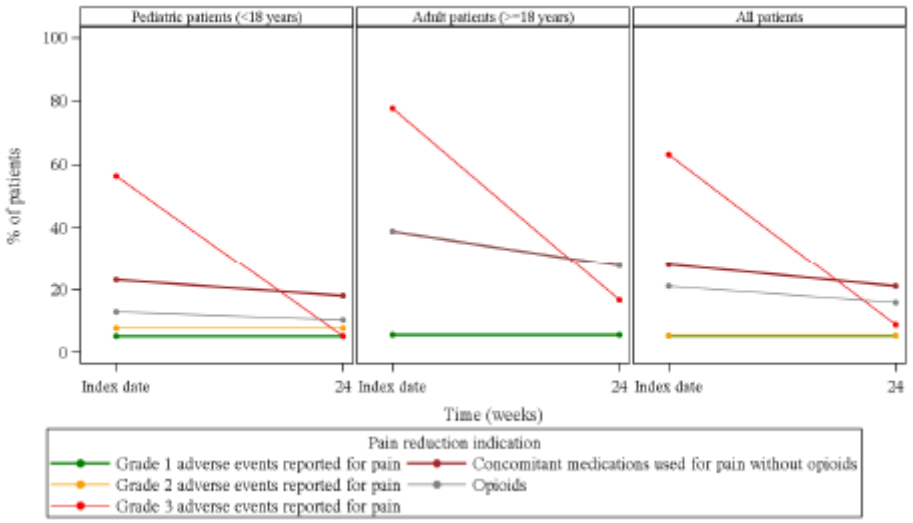
Pain or its management was not consistently reported across patients. To further assess pain reduction at the Week 24 timepoint a composite end point was created.

Pain reduction was considered if **improvement was reported for at least one** of the following items provided that none of the other items was associated with a deterioration during the same period:

- pain score from the questionnaire,

- number of concomitant medications excluding opioids,
- number of opioids,
- number and severity of pain related medical conditions/treatment emergent AEs.

Figure 10 Reduction in pain at Week 24 (Full study population)



Composite endpoint elaborated to assess incidence of pain takes into account: the number of concomitant medications used for pain; opioids used for pain, the severity and number of pain related symptoms and complications, the pain score from the pain severity questionnaire (where available). The figure shows the evolution of each component of the composite endpoint. Adverse events refers to AE and medical conditions pre-existing at index date.
Y axis reports the percentage of patients.
Source: Figure 14.3-1.5

Changes in functional status

Performance status

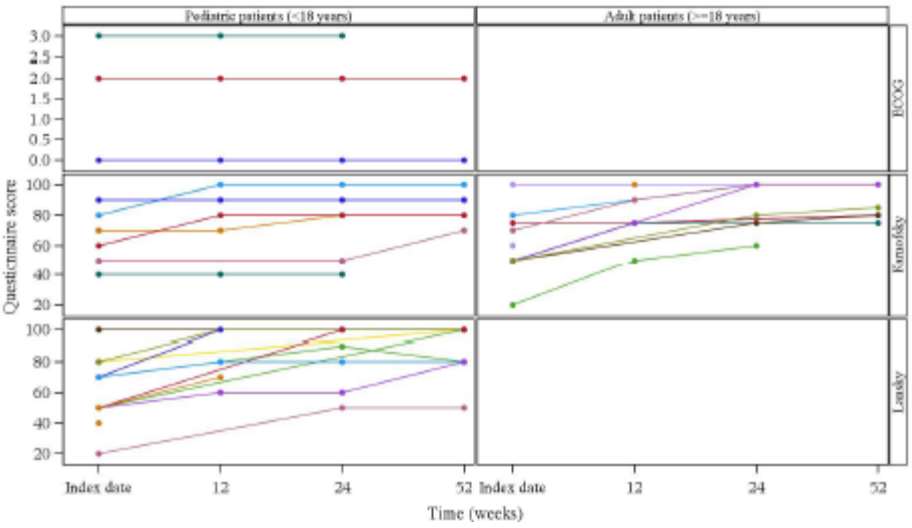
In the overall population, performance status (ECOG, Karnofsky, Lansky) was assessed at the index date for 47 patients (82.5%).

Table 15 Change in performance status score overtime by age category (Full study population)

	Pediatric patients (< 18 years) N=39	Adult patients (≥ 18 years) N=18	All patients N=57
Number of patients with PS at index date - n(%)	33 (84.6)	14 (77.8)	47 (82.5)
Index date - ECOG			
n	3	0	3
Mean (SD)	1.7 (1.53)	NA (NA)	1.7 (1.53)
Median	2.0	NA	2.0
Min-Max	0-3	NA-NA	0-3
Index date – Lansky			
n	24	0	24
Mean (SD)	68.8 (18.01)	NA (NA)	68.8 (18.01)
Median	70.0	NA	70.0
Min-Max	20-100	NA-NA	20-100
Index date – Karnofsky			
n	9	14	23
Mean (SD)	67.8 (15.63)	63.9 (21.85)	65.4 (19.36)
Median	70.0	60.0	70.0
Min-Max	40-90	20-100	20-100
Change in score (% of patients) Week 24			
Stable	9 (27.3)	1 (7.1)	10 (21.3)
Improved	8 (24.2)	6 (42.9)	14 (29.8)

PS: Performance status
Source: Table 14.3-4.1

Figure 11 Change in performance status assessments over time by age category and scale (Full study population)



The graph is showing individual patient data.
The Eastern Cooperative Oncology Group (ECOG) score runs from 0 to 5, with 0 denoting perfect health and 5 death.
The Karnofsky Performance Score (KPS) and Lansky score run from 0 to 100, where 0 is death and 100 is perfect health.
Source: Figure 14.3-1.4

School attendance and work status

School attendance:

School attendance remained unchanged during the study period for the majority of patients. 32 patients (97.0%) at Week 24 and 29 patients (87.9%) at the end of the study had no change in their school

attendance. Improvement in school attendance was reported for one patient (3.0%) at Week 24 and four patients (12.1%) at the end of the study.

Work status:

Work status was reported for 8/18 adult patients (44.4%). Of the total eight patients, part-time (defined as at least one and <35 hours/week) work status was reported for six patients (75%) at the index date.

Work status was stable for six patients (75%) at Week 24 and two patients (25%) at the end of the study. Improvement in work status was reported for five patients (62.5%) at the end of the study.

Changes in healthcare resource use (HRU)

During the 24 weeks of the pre-index period, seven patients (12.3%) were hospitalized, due to PROS.

During the first 24 weeks after the initiation of treatment, six patients (10.5%) were hospitalized due to PROS.

Sixteen patients (28.1%) were hospitalized for any reason while on treatment (median duration of treatment - 19 months), of them 12 patients were hospitalized due to PROS.

Table 16 Health resource utilization during the study period by age category - hospitalization (Full study population)

Characteristic	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (≥18 years) N=18	All patients N=57
Number of patients reporting at least one hospitalization	3 (27.3)	0	7 (43.8)	10 (25.6)	6 (33.3)	16 (28.1)
Number of times a patient has been hospitalized						
n	3	0	7	10	6	16
Mean (SD)	1.0 (0.00)	NA (NA)	2.1 (1.07)	1.8 (1.03)	1.7 (0.82)	1.8 (0.93)
Median	1.0	NA	3.0	1.0	1.5	1.0
Q1-Q3	1.0-1.0	NA-NA	1.0-3.0	1.0-3.0	1.0-2.0	1.0-3.0
Min-Max	1-1	NA-NA	1-3	1-3	1-3	1-3
Duration of hospitalization (days)						
n	3	0	7	10	6	16
Mean (SD)	105.0 (177.54)	NA (NA)	25.6 (21.19)	49.4 (93.68)	22.7 (16.00)	39.4 (74.36)
Median	3.0	NA	21.0	17.0	24.0	19.0
Q1-Q3	2.0-310.0	NA-NA	8.0-32.0	7.0-32.0	6.0-36.0	6.5-34.0
Min-Max	2-310	NA-NA	7-68	2-310	4-42	2-310
Number of times a patient has been hospitalized due to PROS						
n	2	0	6	8	4	12
Mean (SD)	1.0 (0.00)	NA (NA)	1.2 (0.41)	1.1 (0.35)	1.0 (0.00)	1.1 (0.29)
Median	1.0	NA	1.0	1.0	1.0	1.0
Q1-Q3	1.0-1.0	NA-NA	1.0-1.0	1.0-1.0	1.0-1.0	1.0-1.0
Min-Max	1-1	NA-NA	1-2	1-2	1-1	1-2
Number of hospitalizations related to PROS in categories-n (%)						
0	1 (9.1)	0	1 (6.3)	2 (5.1)	2 (11.1)	4 (7.0)
1	2 (18.2)	0	5 (31.3)	7 (17.9)	4 (22.2)	11 (19.3)
2	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Duration of hospitalization related to PROS (days)						
n	2	0	6	8	4	12
Mean (SD)	156.5 (217.08)	NA (NA)	15.7 (10.63)	50.9 (105.18)	13.0 (12.36)	38.3 (86.19)
Median	156.5	NA	13.0	13.0	8.5	9.5
Q1-Q3	3.0-310.0	NA-NA	7.0-26.0	6.0-28.0	5.0-21.0	5.5-28.0
Min-Max	3-310	NA-NA	5-30	3-310	4-31	3-310

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis. Hospitalizations starting on or after the start of study treatment or starting prior to and continuing after the start of study treatment are summarized.
Source: Table 14.3-6.1

Physician narratives

The applicant provided physician narratives for individual patients enrolled in the study (i.e. a generated summary describing the patient's clinical history of PROS, comorbidities, treatment history (medications,

surgeries and medical interventions such as sclerotherapy and endovascular occlusive procedures, and mobility), and discussion on selected target lesions and how their changes correlate with change in function/symptoms and timing of response.

For these narratives, each physician was asked to review the data qualitatively and provide his/her personal assessment of the clinical outcome of the treatment with alpelisib for each individual patient.

Ancillary analyses

Not applicable

3.3.4.3. Summary of main efficacy results

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

Table 17 Summary of efficacy for trial CBYL719F12002 (EPIK-P1)

Title: Retrospective chart review study of patients with PIK3CARelated Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK-P1)			
Study identifier	CBYL719F12002 (EPIK-P1)		
Design	site-based retrospective non-interventional medical chart review		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable not applicable
Hypothesis	Exploratory Efficacy and Safety		
Treatments groups	alpelisib		Adult: 250 mg orally once daily Paediatric patients (2 to <18 years old) 50 mg orally once daily
Endpoints and definitions	Primary endpoint	Responders	Response at week 24 (± 4 weeks) defined by achieving ≥ 20% reduction from the 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 endpoint	sum of measurable target lesion volume	Percentage change over time in the sum of measurable target lesion volume (1 to 3 lesions) at W 24
		sum of All measurable lesion	Percentage change over time in the sum of All measurable (target and non-target) lesion volume at W 24

Title: Retrospective chart review study of patients with PIK3CARelated Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK-P1)			
Study identifier	CBYL719F12002 (EPIK-P1)		
		measurable non-target lesion volume	Percentage change over time in the sum of All measurable non-target lesion volume at W 24
		DoR	Duration of response defined as the time from first documented response (up to week 24), to the date of the first documented disease progression or death due to any cause.
			Changes in type of medication and non-drug therapies (e.g., concomitant PROS-related medications, PROS-related surgeries, duration of treatment/response) over time
			Changes in PROS signs and symptoms, functional status, HRU, and in clinical assessments such as laboratory evaluation, vital signs and physical findings over time.
			Assessment of adverse events for measuring the safety and tolerability of alpelisib.
Database lock	09-Mar-2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**complete cases population** : was a subset of the Efficacy population 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.		
Descriptive statistics and estimate variability	Treatment group	alpelisib	
	Number of subject	32	
	Responders %	37.5%	95% CI 21.2, 86.3
	measurable target lesion volume [mean (SD)]	-13.66%	SD 18.921
	measurable lesion volume [mean (SD)]	no measurable non-target lesions were identified	

Title: Retrospective chart review study of patients with PIK3CARelated Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK-P1)			
Study identifier	CBYL719F12002 (EPIK-P1)		
	measurable non-target lesion volume [mean (SD)]	no measurable non-target lesions were identified	
	DoR	NC	NC
Notes			

3.3.4.4. Clinical studies in special populations

Clinical studies in the elderly

Not performed.

Clinical studies in paediatric patients with renal or hepatic impairment

Not performed.

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

3.3.4.7. Supportive study(ies)

EPIK-P3

EPIK-P3 is a phase II study evaluating the long-term safety and efficacy of alpelisib in patients with PIK3CA-Related Overgrowth Spectrum (PROS) who previously participated in Study CBYL719F12002 (EPIK-P1)

The EPIK-P3 study consists of two study periods:

- an initial retrospective (non-interventional) period, which started on 10-Mar-2020 (one day after the EPIK-P1 data cut-off date) and lasted up to the initiation of the prospective period,
- a prospective period in which safety and efficacy data will be prospectively collected following a structured plan. This interventional study period will start on the day of the first interventional dose administration and will end after all participants have completed at least 5 years of treatment in the prospective period of the study or discontinued earlier, whichever occurs first.

Only the first interpretable results for the final analysis of the retrospective period are available.

EPIK P3 included paediatric and adult participants who participated in EPIK-P1 and continued to receive treatment with alpelisib after the EPIK-P1 cut-off date (i.e. 09-Mar-2020) in the context of the global compassionate use program.

Of the 57 patients who previously participated in EPIK-P1, 52 were eligible for participation in EPIK-P3, 48 (34 paediatrics, 14 adults) of them consented to inclusion in total

. The median duration of exposure (from the start (10-Mar-2020) to the end of the retrospective period) to alpelisib in EPIK-P3 was 24.6 months overall (Min: 12 – Max: 28). The median duration of exposure since the start of alpelisib in EPIK-P1 (for all patients who participated in EPIK-P3) up to the end of the retrospective period of EPIK-P3 was 43.5 months overall (Min: 29 – Max: 75).

The response was assessed in terms of the overall clinical response, which is a combination of clinical evaluation of the patient's general conditions and radiological imaging, and the overall lesion response, which is based on radiological imaging and other methods of measurement (e.g., circumference measured by rulers). The response to alpelisib was assessed by the investigators with a single evaluation.

Results:

Table 18 shows the overall clinical response, and the overall lesion response relative to before alpelisib initiation in EPIK-P1, most patients experienced improvement relative to the start of alpelisib

Table 18 Proportion of patients with improved/stable/worsening overall clinical response and overall lesion response during the retrospective period by age category (FASR)

	Age at initiation of alpelisib					
	2-5 years N=11 n (%)	6-11 years N=10 n (%)	12-17 years N=13 n (%)	Pediatric patients (<18 years) N=34 n (%)	Adult patients (>=18 years) N=14 n (%)	All patients N=48 n (%)
Overall clinical response-n (%)						
Improved	8 (72.7)	9 (90.0)	9 (69.2)	26 (76.5)	8 (57.1)	34 (70.8)
Stable	3 (27.3)	1 (10.0)	2 (15.4)	6 (17.6)	5 (35.7)	11 (22.9)
Worsened	0	0	2 (15.4)	2 (5.9)	1 (7.1)	3 (6.3)
Overall lesion response-n (%)						
Improved	11 (100.0)	9 (90.0)	11 (84.6)	31 (91.2)	7 (50.0)	38 (79.2)
Stable	0	0	2 (15.4)	2 (5.9)	5 (35.7)	7 (14.6)
Worsened	0	0	0	0	1 (7.1)	1 (2.1)
Non-evaluable	0	1 (10.0)	0	1 (2.9)	1 (7.1)	2 (4.2)

Age categories are based on the derived age at the initiation of alpelisib in the global compassionate use program.
The assessment is relative to before the patient started taking alpelisib in the global compassionate use program.
Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
Source: CSR Post-text Tables 14.2-1.1, 14.2-1.2

Table **19** shows the proportion of patients with improvement/stabilization (relative to the start of the retrospective period) in PROS-related signs and symptoms by the end of the retrospective period for vascular malformation.

Most patients experienced a stabilisation in their PROS-related signs and symptoms during the retrospective period

Table 19 Most frequent PROS-related signs and symptoms during the retrospective period (FASR)

	Age at initiation of alpelisib								
	Pediatric patients (<18 years) N=34			Adult patients (>=18 years) N=14			All patients N=48		
Preferred term	Start retrosp. period n (%)	Improved[a] by End retrosp. period n (%)	Stable[b] at End retrosp. period n (%)	Start retrosp. period n (%)	Improved[a] by End retrosp. period n (%)	Stable[b] at End retrosp. period n (%)	Start retrosp. period n (%)	Improved[a] by End retrosp. period n (%)	Stable[b] at End retrosp. period n(%)
Vascular malformation	21 (61.8)	1 (4.8)	20 (95.2)	11 (78.6)	1 (9.1)	9 (81.8)	32 (66.7)	2 (6.3)	29 (90.6)
Limb asymmetry	16 (47.1)	1 (6.3)	15 (93.8)	12 (85.7)	2 (16.7)	9 (75.0)	28 (58.3)	3 (10.7)	24 (85.7)
Lipomatosis	13 (38.2)	2 (15.4)	11 (84.6)	4 (28.6)	0	4 (100)	17 (35.4)	2 (11.8)	15 (88.2)
Hypertrophy	13 (38.2)	3 (23.1)	10 (76.9)	2 (14.3)	1 (50.0)	1 (50.0)	15 (31.3)	4 (26.7)	11 (73.3)
Lipoma	12 (35.3)	0	12 (100)	3 (21.4)	0	3 (100)	15 (31.3)	0	15 (100)
Scoliosis	9 (26.5)	1 (11.1)	8 (88.9)	4 (28.6)	0	4 (100)	13 (27.1)	1 (7.7)	12 (92.3)
Disseminated intravascular coagulation	4 (11.8)	0	4 (100)	8 (57.1)	0	8 (100)	12 (25.0)	0	12 (100)
Venolymphatic malformation	9 (26.5)	1 (11.1)	7 (77.8)	3 (21.4)	0	2 (66.7)	12 (25.0)	1 (8.3)	9 (75.0)
Developmental delay	10 (29.4)	0	10 (100)	0	0	0	10 (20.8)	0	10 (100)

Age categories are based on the derived age at the initiation of alpelisib in the global compassionate use program.
Conditions at the start of the retrospective period correspond to the ongoing medical conditions related to PROS at the end of EPIK-P1 study (09-Mar-2020).
a Improvement is defined based on CTC grade reduction or resolution of the event as compared to the start of the retrospective period.
b Stabilization is defined based on no change in CTC grade as compared to the start of the retrospective period. % are calculated on the number of patients reporting the event at start of the retrospective period.
Source: CSR post-Text Table 14.3-2.9

No patient had surgery due to disease progression during the retrospective period of EPIK-P3. Notably, four paediatric patients were able to undergo surgery due to disease improvement.

3.3.5. Discussion on clinical efficacy

The applicant applies for a conditional MAA 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** PIK3CA related overgrowth spectrum (PROS) **who require systemic therapy**."

Pending the outcome of the LoOI, the indication can be subject to change.

Design and conduct of clinical study

The application is based on a single retrospective study of patients with PIK3CA Related Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK P1).

Since 2016, alpelisib was used as part of a compassionate use program in France (nominative Temporary Authorisation for Use (ATU) and *Venot et al (2018)* described how alpelisib was used to treat 19 patients with PROS at a single centre. Given the number of compassionate use requests following the publication, the applicant issued a global Managed Access Program (MAP; Treatment Plan) in Nov-2018 extending the treatment to additional patients worldwide. A treatment plan was generated to serve as a guidance document for the treatment and monitoring of patients under this MAP. Patients in France continued to receive alpelisib through the ATU.

EPIK P1 was a retrospective chart review of patients 2 years of age and older with severe or life-threatening PROS who have received alpelisib as part of a compassionate use program at select sites. EPIK P1 aimed to collect structured data from medical charts across different sites and describes 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.

At the time of Protocol Assistance (PA) it was stated that the proposed mitigation plans for EPKI-P1 were not deemed sufficient to compensate for the lack of prospective comparative data.

Due to the absence of approved medical treatment and the severity of the condition, the applicant considered unethical to conduct a placebo-controlled study.

The **population** consisted of patients aged 2 years old and above who received at least one dose of alpelisib through the compassionate use program. The treatment had to be initiated at least 24 weeks before the abstraction date.

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 during the ATU program 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).

No paediatric PK data are available as results of the double-blind phase II study, 16-week randomized, placebo controlled period, that aim to assess the efficacy, safety and PK of alpelisib in paediatric and adult patients with PROS (EPIK-P2) are expected in 2024.

The applicant subsequently recommends for this application the same dosage regimen as used in its global compassionate use program.

However, the proposed posology in Section 4.2 of the SmPC differs somewhat of that recommended in the compassionate use program and it is uncertain if the current proposal is substantiated by the actual use of alpelisib in clinical practice.

Per MAP Treatment Plan, alpelisib was administered, in adult patients, at a starting dose of 250 mg orally once daily which could be adjusted for toxicity. In paediatric patients, alpelisib was administered at a starting dose of 50 mg orally once daily and no dose reduction was allowed. The treatment plan for the ATU states that "the posology will be determined by the prescriber based on the patient's need". As 50/57 patients were treated through ATU, the applicant should specify the doses received by the all patients treated in this context (new **OC**).

Initially, the 19 patients in Venot et al 2018, were recommended to take alpelisib without food (in the morning before breakfast). Since July 2018 for patients treated under the ATU and since September 2018 for patients treated under the MAP, it was recommended to take alpelisib with food. Considering that the number of patients in each group is low, that for some patients the information is not known

and that recommendations change along the EPIK-P1 study, no firm conclusion can be drawn and the proposed recommendation to administer alpelisib with food can be acknowledged based on clinical pharmacology data showing that alpelisib has a positive food effect at high doses.

The SmPC proposes a dose increase to 125 mg once in paediatric patients ≥6 years old for response optimisation (clinical/radiological) after 24 weeks of treatment. During the compassionate use, some patients had a dose increase to 100 mg or 150 mg but no paediatric patients had an increase in dose to 125 mg. The potential gain in efficacy when increasing the dose from 50 to 125 mg is not established (**OC**).

The applicant did not develop a specific pharmaceutical form such as liquid or granule formulations suitable for children whereas children as young as 2 years old were to be treated. The SmPC proposes in section 4.2 that the tablets should be administered as an oral suspension in patients who are not able to swallow tablets. The Applicant recognizes that the ATU did not provide a recommendation for alpelisib to be administered as an oral suspension and could not provide data how alpelisib was administrated to youngest patients, thus no efficacy/safety data are available regarding the use of alpelisib as an oral suspension (PK and safety **OC**).

Section 4.2 of the SmPC provides extensive recommendations for treatment dose modifications or discontinuation due to toxicity. However, no such recommendations exist for subjects who experience no efficacy at all. The Applicant is required to discuss if based on the totality of the evidence available any guidance for reassessing the pertinence of continuing treatment can be given to the prescribing physicians (**OC**).

Objectives/endpoints. It is acknowledged that there is no validated criteria to objectively assess the changes in PROS lesions that could have been used for the assessment of the efficacy of alpelisib in PROS

The **primary** endpoint was defined as a reduction ≥ 20% in the sum of measurable target lesion volumes (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.

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 volumes, changes in the sum of all measurable (target and non-target) lesion volumes over time, changes in the sum of all measurable non-target lesion volumes over time and DoR are, similar to the primary endpoint, based on the independent central radiology review.

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. However, the clinical endpoints used are not validated for, or reliable measures specific to, the target population. Furthermore, due to the open-label retrospective design of the study, the lack of a comparator treatment arm and the small sample size, the interpretability of these endpoints could be challenging.

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 :

In its response to the D120 CHMP list of questions, the Applicant provided the first results of the retrospective part of a phase II study 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.

Of the 57 patients who previously participated in EPIK-P1, 52 were eligible for participation in EPIK-P3 (at least one dose of alpelisib after the EPIK-P1 cut-off date (09-Mar-2020)), and 48 (34 paediatrics, 14 adults) were included in the retrospective period of EPIK-P3. Median duration of exposure to the end of the retrospective period to alpelisib was 24.6 months overall (Min: 12 – Max: 28). Median duration of exposure since the start of alpelisib in EPIK-P1 up to the end of the retrospective period of EPIK-P3 was 43.5 months overall (Min: 29 – Max: 75).

The response to alpelisib was assessed by the investigators with a single evaluation, 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).

Efficacy data and additional analyses

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. Patients were recruited in 7 sites across 5 countries however most patients (44/52 77.2%) were included in one centre in France.

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.

Most of the patients were female (33 patients, 57.9%).

The most reported subtype 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%).

In the paediatric population, CLOVES and MCAP subtypes were concomitantly reported in four patients. Two patients included in the 'other' category had lipomatosis with pseudoartrogriposis, without vascular anomaly and mixed vascular malformations (lymphatic and venous).

For most patients, race and ethnicity were not reported mostly due to the French regulation; however the EPAR of Piqray states that "the impact of ethnicity found in the Phase I popPK analysis was tested in the Phase III population PK model and was not found to be significant."

Results Primary endpoint

The primary endpoint was evaluated on the complete cases population, a subset of the efficacy population which included 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. 32 out of 57 treated patients fulfilling 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 open label design of the study and the absence of external control, natural history study or historical data.

Subgroup 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 subtypes. The applicant is requested to substantiate how the efficacy results, only observed in the CLOVES subtype, can be generalized to the other subtypes (**MO**).

In addition, in the Clinical Summary of Efficacy the following is stated: "the primary efficacy endpoint was reported for the following subgroups: age; sex; mutation type; PROS subtype; and lesion type (i.e. vascular, adipose), and the following additional subgroup analyses of the primary endpoint were performed: prior treatment status regarding therapies targeting the PI3K-AKT-mTOR pathway; body weight in paediatric patients; index date diabetic status.

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 subgroup analyses were conducted on the effect of treatment by tissue type, but rather by the anatomical location site. This limitation adds further uncertainty to the actual demonstration of benefit of alpelisib in the treatment of PROS and raises serious doubts on whether some benefit could be expected across the broad spectrum of PROS and patients regardless of the type of tissue affected (MO). Plans to collect this information in the EPIK-P2 study are welcome.

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 PK data in this group raises the question of the appropriateness of the chosen dose in this group (**OC**).

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 volumes 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 (see dosing question in paediatric population).

Concomitant PROS-related medications

Overall, during the course of treatment with alpelisib the number of patients taking at least one medication lowered during treatment (index date: 40/57 patients, 70.2%; Week 24: 37/56, 66.1%; end of study 31/57 patients, 54.4%).

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.

PROS related surgery

From diagnosis to pre-index date period, most patients (87.7%) had at least one PROS related surgery. Disease progression was the main reason for surgery (92.2% surgeries in the overall population).

During the 24 weeks pre-index period, 5 patients (8.5%) had at least one surgery, all related to disease progression. During the study period, 12 surgery procedures were performed in 7 patients (12.3%). The reasons were: disease progression (25%), disease improvement (25%), and "other" (50%).

Given that during the 24 weeks study period, the same proportion of surgery procedures were performed due to disease progression or disease improvement, it is difficult to conclude on the effect of alpelisib on PROS-related surgery.

However, there seems to be less surgery after the start of treatment compared to the period from diagnosis to the index date.

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.

The applicant also created a composite endpoint including questionnaire, use of pain medication and pain related medical conditions/treatment emergent AEs. A reduction in grade 3 pain-related medical conditions or grade 3 AEs was reported in patients over time. It worth noted that this composite endpoint was implemented to the SAP on 31-Mar-2021 before the database lock date (28-May-2021) but after the initiation of data collection (09-Jun-2020) which may have resulted in bias.

Performance status at index time was available for 47 patients (82.5%), and at week 24 data were available for 24 patients. It was improved in 14 patients (21.3%) and stable in 10 patients (29.8%). However, the clinical relevance of this improvement is not clear. Given the design of the study and the high rate of missing data, no firm conclusion can be drawn.

The school attendance was reported for 33 patients and remained stable during the study. Working status was reported for only 8 patients. Therefore, no meaningful conclusions can be drawn.

The number of hospitalization due to PROS complication was comparable during the 24 weeks pre index period (7 patients, 12%) and the study period (6 patients, 10.5%).

Vital signs such as blood pressure, ECG, haematology and clinical chemistry were collected as part of efficacy endpoints. The clinical relevance of those data in the context of the PROS symptoms is unclear.

Supportive study EPIK-P3

The results of the 48 patients who completed the EPIK-P1, continued treatment after the 9th March 2020 cut-off date and consented to participate in this retrospective data collection, show an overall clinical response of improvement from the start of alpelisib in 34/48 (70.8%), of stable disease in 11/48 (22.9%), and of worsening in 3/48 (6.3%) of patients. The overall lesion response was improved in 38/48 (79.2%), stable in 7/48 (14.6%), and worsened in 1/48 (2.1%) patients.

Most patients reported stabilization in PROS-related signs and symptoms by the end of the retrospective period (relative to the start of the retrospective period) for vascular malformation (90.6%), for limb asymmetry was (85.7%), and for lipomatosis was (88.2%). On the same period, the proportion of patients with improvement for vascular malformation was 6.3%, for limb asymmetry was 10.7%, and for lipomatosis was 11.8% in all patients

No patient had surgery due to disease progression during the retrospective period of EPIK-P3. Notably, four paediatric patients were able to undergo surgery due to disease improvement.

The EPIK-P3 results show that most patients 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 48 patients represent the most favourable selected

subset within the total treated population of 58 patients, 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. These limitations should be borne in mind in the interpretation of the study results.

Additional expert consultation

In light of the rarity of the disease, the retrospective nature of the pivotal study, study design, and the lack of comparator (internal or external), it is likely that uncertainties will remain; the need to consult an Ad Hoc Expert Group (AHEG) AHEG should be discussed by the CHMP.

Additional efficacy data needed in the context of a conditional MA

The applicant is requesting a CMA for Vijoice for the treatment of adult and paediatric patients aged 2 years and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS).

Alpelisib falls within the scope of a CMA, as PROS is a seriously debilitating and life-threatening disease (Article 2 (1)) and is an orphan medicinal product (Article 2 (3)) (EMA/OD/0000047280).

The applicant's proposal to provide additional efficacy/safety data follows:

EPIK-P2 Trial: A prospective clinical Phase II study in patients 2 years and older with PROS (as agreed in the PIP). EPIK-P2 is a multicenter study with an upfront 16-week, randomized, double-blind, placebo-controlled period, and extension periods to assess the efficacy, safety, and PK of alpelisib in paediatric and adult participants with PROS (with symptomatic and/or progressive overgrowth and at least one measurable PROS-related lesion). In the confirmatory part of EPIK-P2, 156 participants, 78 adults and 78 children and adolescents, are planned to be enrolled. The study will have an overall follow-up of approximately 5 years to collect long-term safety and efficacy data. The first patient first visit (FPFV) in this study was achieved on 19-Apr-2021. As of June 2022, 79 subject had been enrolled. Planned submission of the study results (PEP) is expected by Q2/3 2024 (Q12024 best case scenario).

Update on EPIK P2:

As of 03-Jan-2023, the EPIK-P2 Study, a double-blind, randomised placebo-controlled study, has recruited 150 out of 156 patients planned, and the CSR for the primary analysis is expected to be available in ~Mar-2024 and will afterwards be submitted for review. The final analysis CSR for EPIK-P2 is expected to be available in ~ Sep-2030.

Study EPIK-P3: A Phase II multicenter, interventional, open-label study in paediatric and adult patients with PROS who participated in EPIK-P1, and who continued to receive treatment with alpelisib after the EPIK-P1 cut-off date (i.e., 09-Mar-2020). The study has an initial retrospective period and a subsequent prospective period. It is expected that approximately 50 patients may be enrolled in EPIK-P3; the final number of patients in EPIK-P3 will depend on the number of EPIK-P1 patients who continued to receive treatment with alpelisib after the cut-off date was applied for EPIK-P1 and who will provide their consent for EPIK-P3. The purpose of this study is to assess the long-term safety and efficacy of alpelisib treatment. The patients will have data collected for approximately 2 years in the retrospective period and will be followed up for at least 5 years in the prospective period. First Retrospective data would be expected by the end of 2022.

Update on EPIK P3:

The first interpretable results of the retrospective period only have been presented. The prospective (interventional) period is ongoing, enrolment is complete (40 patients) and will assess the long-term

(1st IA at 1 year, 2nd IA 3 years, final results 5 years) safety and tolerability of alpelisib over time. The CSRs are expected to be available in ~Sep-2024 (1st IA) and ~Sep-2026 (2nd IA), with final CSR expected to be available ~Sep-2028.

At this stage, the product is not recommended for a conditional marketing authorisation as the benefit-risk balance is currently unknown (as discussed).

3.3.6. Conclusions on clinical efficacy

There is a solid 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 (now commonly known as PROS). Alpelisib is an α-specific PI3K inhibitor, which has shown benefit in solid tumours (breast cancer), as well as in *in vitro* and *in vivo* nonclinical models of PROS.

Data suggest that the tumour reduction observed in patients with PROS might be attributable to alpelisib based on the ICRR review.

However, the benefits/risk balance is currently uncertain as:

- the exact effect of alpelisib on the rate of progression of PROS is unclear considering that neither the rate of progression of PROS in patients prior to the initiation of treatment, nor natural history study or bibliographic data have been provided and that, importantly, there was no control group in EPIK-P1;
- no clear correlation has been established between tumour decrease and the clinical outcome although a positive trend was reported in symptoms/signs;
- the extrapolation of the effects observed in CLOVES patients to the entire PROS population requires further justification;
- there is no available information on the actual results according to the tissue type (i.e. vascular, adipose),
- the number of documented patients included in the application is low;
- uncertainties remain regarding the proposed dosage in the paediatric population.

3.3.7. Clinical safety

Alpelisib safety profile is based on one pivotal study EPIK-P1, a retrospective chart review study performed with 57 PROS patients aged 2 years and older. Eligible patients had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and had documented evidence of mutation in the PIK3CA gene. PROS belongs to orphan diseases and no treatment are currently available. In this way and due to the retrospective nature of data collection, there is no comparator arm and missing data were expected to be common. Hence, as a conservative approach, the applicant has established imputation rules for treatment-emergent adverse events, notably missing data.

The safety evaluation of alpelisib in PROS also takes into account safety data reported to the Novartis Global Safety Database (ARGUS) from the PROS compassionate use programs under which approximately 385 patients (including 242 paediatric) received treatment across over 20 countries as of 28-Feb-2022 (see section 4.12 Post-Marketing experiences).

Recently, alpelisib in combination with fulvestrant was approved on 27 July 2020 by EU for the treatment of locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy. The recommended dose in patients with advanced or metastatic breast cancer is 300 mg (two 150 mg tablets) taken orally once daily with food in combination with fulvestrant.

As supportive, safety data from 3 studies carried out in adult patients with advanced solid malignancies have been supplied:

- Study X2101: a Phase IA, multicentre, open-label dose escalation study of oral alpelisib, in adult patients with advanced solid malignancies whose tumours have an alteration of the PIK3CA gene.

- Study X1101: a Phase I study of BYL719 in Japanese adult patients with advanced solid malignancies.

- SOLAR-1: a Phase III randomized double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment.

However, due to different patient populations, indications and posology, safety data can be neither pooled nor compared with those reported in EPIK-P1 study.

Besides, 3 clinical studies in PROS are ongoing:

- EPIK-P2 (CBYL719F12201): 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 paediatric (≥ 2 years) and adult patients with PROS, is currently ongoing. The first patient first visit in this study was achieved on 19-Apr-2021. A cut-off date of 12-Nov-2021 was applied for the first DMC safety review at which time 26 patients were randomized and treated for a median duration of approximately 3 weeks. Based on their review of the unblinded data, the DMC indicated that there were no safety issues and that it was ethical to continue the study as planned.

- EPIK-P3 (CBYL719F12401): a Phase II multi-center, interventional (preceded by a retrospective non-interventional period), open label study in paediatric and adult patients with severe or life-threatening complications of PROS who were treated with alpelisib as part of a compassionate use program, who previously participated in EPIK-P1, and who continued to receive treatment with alpelisib after the EPIK-P1 cut-off date (i.e., 09-Mar-2020). The purpose of this study was to assess the long-term safety and efficacy of alpelisib treatment. The first patient, first visit was achieved on 27-Jan-2022.

- BE study (CBYL719F12101): a single-center, randomized, open-label, three period crossover study to investigate the bioequivalence of alpelisib granule and film-coated tablet formulation, and the food effect of alpelisib granule formulation in adult healthy volunteers. The first patient, first visit was achieved on 03-Feb-2022.

Both EPIK-P2 and EPIK-P3 are proposed by the applicant as additional pharmacovigilance activities that allow the monitoring of alpelisib safety with a long term-use including effects on growth and development.

3.3.7.1. Patient exposure

Overall, fifty-seven (n=57) patients were enrolled across seven sites in five countries: France (n=50), Spain (n=3), US (n=2), Ireland (n=1), and Australia (n=1). The number of patients was distributed as follows: n=39 paediatric patients and n=18 adult patients.

The median duration of exposure to alpelisib in paediatric and adult populations was 18 months and 19.2 months, respectively. Eighty-three percent (83%) adult patients and 77% paediatric patients were exposed to alpelisib therapy for at least 12 months.

According to the last PSUSA (EMEA/H/C/PSUSA/00010871/202111) for alpelisib (Piqray®) indicated in the treatment of locally advanced or metastatic breast cancer, cumulatively a total of 5 765 patients have been treated with alpelisib in clinical trials. Post-marketing, the cumulative estimated exposure was 4 623 patients-years worldwide (of which 564 patient-years in the EU).

Most of patients was female in the paediatric population (61.5%) and the gender was balanced in adult patients (50% for each category). The overall median BMI was 20.2 kg/m^2.

The performance status scores (Lansky or Karnofsky score) were evaluated for 33 paediatric patients (84.6%) at the index date and 21 patients had a performance status ≤ 70. The performance status scores were evaluated for 14 adult patients (77.8%) at the index date and nine patients had a Karnofsky score ≤ 70.

The average daily dose received was 50 mg in paediatric patients and 250 mg in adult patients.

3.3.7.2. Adverse events

The table 10-27 summarizes the overall adverse events by age category:

Table 10-27 Overview of adverse events by age category (Full study population)

	2-5 years N=11 n (%)		6-11 years N=12 n (%)		12-17 years N=16 n (%)		Pediatric patients (<18 years) N=39 n (%)		Adult patients (≥ 18 years) N=18 n (%)		All patients N=57 n (%)	
Category	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Adverse events	9 (81.8)	1 (9.1)	9 (75.0)	0	13 (81.3)	3 (18.8)	31 (79.5)	4 (10.3)	16 (88.9)	9 (50.0)	47 (82.5)	13 (22.8)
Treatment-related	2 (18.2)	0	3 (25.0)	0	4 (25.0)	0	9 (23.1)	0	13 (72.2)	1 (5.6)	22 (38.6)	1 (1.8)
SAEs	3 (27.3)	1 (9.1)	2 (16.7)	0	5 (31.3)	2 (12.5)	10 (25.6)	3 (7.7)	11 (61.1)	9 (50.0)	21 (36.8)	12 (21.1)
Treatment-related	0	0	0	0	0	0	0	0	3 (16.7)	1 (5.6)	3 (5.3)	1 (1.8)
AEs leading to dose reduction	0	0	0	0	0	0	0	0	3 (16.7)	0	3 (5.3)	0
Treatment-related	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
AEs leading to dose interruption	0	0	1 (8.3)	0	1 (6.3)	0	2 (5.1)	0	3 (16.7)	2 (11.1)	5 (8.8)	2 (3.5)
Treatment-related	0	0	0	0	1 (6.3)	0	1 (2.6)	0	2 (11.1)	1 (5.6)	3 (5.3)	1 (1.8)

Numbers (n) represent counts of patients. Number (N) represents 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 24.0, CTCAE version 4.03. Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.

All grades includes any AEs with missing grade.

Source: Tables 14.3.1-1.1, 14.3.1-1.2,14.3.1-1.6, 14.3.1-1.7, 14.3.1-1.8, 14.3.1-1.9, 14.3.1-1.10,14.3.1-1.11.

The table 10-28 summarizes adverse events experienced in the patient populations by system organ class and according to age and category:

Table 10-28 Adverse events irrespective of study treatment relationship by system organ class and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Primary system organ class	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	9 (81.8)	1 (9.1)	9 (75.0)	0	13 (81.3)	3 (18.8)	31 (79.5)	4 (10.3)	16 (88.9)	9 (50.0)	47 (82.5)	13 (22.8)
Gastrointestinal disorders	3 (27.3)	0	5 (41.7)	0	4 (25.0)	0	12 (30.8)	0	8 (44.4)	1 (5.6)	20 (35.1)	1 (1.8)
General disorders and administration site conditions	3 (27.3)	0	1 (8.3)	0	5 (31.3)	0	9 (23.1)	0	4 (22.2)	2 (11.1)	13 (22.8)	2 (3.5)
Infections and infestations	3 (27.3)	0	2 (16.7)	0	4 (25.0)	2 (12.5)	9 (23.1)	2 (5.1)	4 (22.2)	2 (11.1)	13 (22.8)	4 (7.0)
Metabolism and nutrition disorders	2 (18.2)	0	1 (8.3)	0	3 (18.8)	0	6 (15.4)	0	6 (33.3)	1 (5.6)	12 (21.1)	1 (1.8)
Skin and subcutaneous tissue disorders	0	0	0	0	2 (12.5)	0	2 (5.1)	0	10 (55.6)	0	12 (21.1)	0
Nervous system disorders	1 (9.1)	0	2 (16.7)	0	2 (12.5)	0	5 (12.8)	0	5 (27.8)	0	10 (17.5)	0
Blood and lymphatic system disorders	1 (9.1)	0	1 (8.3)	0	2 (12.5)	0	4 (10.3)	0	4 (22.2)	1 (5.6)	8 (14.0)	1 (1.8)
Musculoskeletal and connective tissue disorders	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	1 (5.6)	7 (12.3)	1 (1.8)
Respiratory, thoracic and mediastinal disorders	2 (18.2)	1 (9.1)	2 (16.7)	0	0	0	4 (10.3)	1 (2.6)	3 (16.7)	1 (5.6)	7 (12.3)	2 (3.5)
Vascular disorders	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Reproductive system and breast disorders	0	0	0	0	1 (6.3)	0	1 (2.6)	0	5 (27.8)	1 (5.6)	6 (10.5)	1 (1.8)
Congenital, familial and genetic disorders	1 (9.1)	0	1 (8.3)	0	2 (12.5)	0	4 (10.3)	0	0	0	4 (7.0)	0
Injury, poisoning and procedural complications	1 (9.1)	0	0	0	1 (6.3)	0	2 (5.1)	0	2 (11.1)	1 (5.6)	4 (7.0)	1 (1.8)
Endocrine disorders	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	2 (11.1)	0	3 (5.3)	1 (1.8)
Investigations	1 (9.1)	0	1 (8.3)	0	0	0	2 (5.1)	0	1 (5.6)	0	3 (5.3)	0
Psychiatric disorders	0	0	0	0	1 (6.3)	0	1 (2.6)	0	1 (5.6)	0	2 (3.5)	0
Cardiac disorders	0	0	0	0	1 (6.3)	0	1 (2.6)	0	0	0	1 (1.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Renal and urinary disorders	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
A patient with multiple severity grades for a SOC is only counted under the maximum grade.
Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.
Adverse events reported are intended as treatment emergent events.
MedDRA version 24.0, CTCAE version 4.03.
Source: Table 14.3.1-1.1

The table 10-29 summarizes adverse events experienced in the patient populations by preferred term class and according to age and category:

Table 10-29 Adverse events (any grade more than 5% or reported by at least 1 patient as grade 3 or higher in the overall population) irrespective of study treatment relationship by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	9 (81.8)	1 (9.1)	9 (75.0)	0	13 (81.3)	3 (18.8)	31 (79.5)	4 (10.3)	16 (88.9)	9 (50.0)	47 (82.5)	13 (22.8)
Diarrhoea	1 (9.1)	0	3 (25.0)	0	1 (6.3)	0	5 (12.8)	0	4 (22.2)	0	9 (15.8)	0
Hyperglycaemia	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Aphthous ulcer	1 (9.1)	0	1 (8.3)	0	1 (6.3)	0	3 (7.7)	0	3 (16.7)	0	6 (10.5)	0
Disseminated intravascular coagulation	0	0	1 (8.3)	0	1 (6.3)	0	2 (5.1)	0	3 (16.7)	1 (5.6)	5 (8.8)	1 (1.8)
Inflammation	2 (18.2)	0	0	0	1 (6.3)	0	3 (7.7)	0	2 (11.1)	1 (5.6)	5 (8.8)	1 (1.8)
Dry skin	0	0	0	0	1 (6.3)	0	1 (2.6)	0	3 (16.7)	0	4 (7.0)	0
Eczema	0	0	0	0	1 (6.3)	0	1 (2.6)	0	3 (16.7)	0	4 (7.0)	0
Vascular malformation	1 (9.1)	0	1 (8.3)	0	2 (12.5)	0	4 (10.3)	0	0	0	4 (7.0)	0
Alopecia	0	0	0	0	0	0	0	0	3 (16.7)	0	3 (5.3)	0
Cellulitis	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	2 (11.1)	1 (5.6)	3 (5.3)	2 (3.5)
Gait disturbance	1 (9.1)	0	1 (8.3)	0	0	0	2 (5.1)	0	1 (5.6)	0	3 (5.3)	0
Headache	0	0	0	0	0	0	0	0	3 (16.7)	0	3 (5.3)	0
Hypoglycaemia	1 (9.1)	0	0	0	2 (12.5)	0	3 (7.7)	0	0	0	3 (5.3)	0
Pain in extremity	0	0	0	0	1 (6.3)	0	1 (2.6)	0	2 (11.1)	1 (5.6)	3 (5.3)	1 (1.8)
Stomatitis	1 (9.1)	0	2 (16.7)	0	0	0	3 (7.7)	0	0	0	3 (5.3)	0
Dehydration	0	0	1 (8.3)	0	0	0	1 (2.6)	0	1 (5.6)	1 (5.6)	2 (3.5)	1 (1.8)
Adrenal insufficiency	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	0	0	1 (1.8)	1 (1.8)
Dyspnoea	1 (9.1)	1 (9.1)	0	0	0	0	1 (2.6)	1 (2.6)	0	0	1 (1.8)	1 (1.8)
Fall	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Impaired healing	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Multiple fractures	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Pulmonary embolism	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Renal impairment	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Streptococcal sepsis	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Vaginal haemorrhage	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Volvulus	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Wound infection	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	0	0	1 (1.8)	1 (1.8)

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.
Adverse events reported are intended as treatment emergent events.
MedDRA version 24.0, CTCAE version 4.03.
Source: Table 14.3.1-1.1

▪ Adverse events suspected to be related to alpelisib

Table 2.2 summarizes adverse reactions by SOC and PTs:

Table 2-2 **Adverse events (any grade >5% or reported by at least one patient as grade 3 or higher in all patients), suspected to be study treatment related by preferred term and age category (Full study population)**

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	2 (18.2)	0	3 (25.0)	0	4 (25.0)	0	9 (23.1)	0	13 (72.2)	1 (5.6)	22 (38.6)	1 (1.8)
Hyperglycaemia	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Aphthous ulcer	1 (9.1)	0	1 (8.3)	0	1 (6.3)	0	3 (7.7)	0	3 (16.7)	0	6 (10.5)	0
Alopecia	0	0	0	0	0	0	0	0	3 (16.7)	0	3 (5.3)	0
Stomatitis	1 (9.1)	0	2 (16.7)	0	0	0	3 (7.7)	0	0	0	3 (5.3)	0
Cellulitis	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)

Numbers (n) represent counts of patients. Number (N) represents total number of patients included in the analysis.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
Treatment emergent adverse events- are, PROS and non–PROS related, events starting during the study period (after or on the index date) or starting prior and worsening during the study period.
Adverse events reported are intended as treatment emergent events.
MedDRA version 24.0, CTCAE version 4.03.
Source: [PROS EPIK-P1-Table 14.3.1-1.2]

- Adverse reactions listed under the section 4.8 of the SmPC: tables 2.6 and 2.7:

Table 2-6 **Adverse reactions by system organ class and preferred term – EPIK-P1 (Full study population)**

Adverse reactions	Pediatric patients N = 39		Adult patients N = 18		All patients N = 57	
	All grades 1-4	Grade 3-4	All grades 1-4	Grade 3-4	All grades 1-4	Grade 3-4
Gastrointestinal disorders						
Diarrhea	13%	0%	22%	0%	16%	0%
Stomatitis [a]	15%	0%	17%	0%	16%	0%
Nausea	2.6%	0%	6%	0%	3.5%	0%
Vomiting	2.6%	0%	6%	0%	3.5%	0%
General disorders and administration site conditions						
Mucosal dryness [b]	2.6%	0%	6%	0%	3.5%	0%
Metabolism and nutrition disorders						
Hyperglycemia	5%	0%	28%	0%	12%	0%
Dehydration	2.6%	0%	6%	6%[d]	3.5%	1.8%[d]
Decreased appetite	0%	0%	6%	0%	1.8%	0%
Nervous system disorders						
Headache	0%	0%	17%	0%	5%	0%
Skin and subcutaneous tissue disorders						
Dry skin	2.6%	0%	17%	0%	7%	0%
Alopecia	0%	0%	17%	0%	5%	0%
Acne [c]	0%	0%	6%	0%	1.8%	0%

Grading according to CTCAE Version 4.03.

[a] Stomatitis: including stomatitis and aphthous ulcer. Mouth ulceration has been reported in PROS patients treated with alpelisib under compassionate use programs outside of EPIK-P1.

[b] Mucosal dryness: including dry mouth and vulvovaginal dryness.

[c] Dermatitis acneiform has been reported in PROS patients treated with alpelisib under compassionate use programs outside of EPIK-P1.

[d] No Grade 4 adverse reactions were reported.

Source: [PROS SCS Appendix 2-Table 17.3-1.2]

Table 2-7 Selected laboratory abnormalities occurring in study EPIK-P1 (Full study population)

Laboratory Abnormality	Pediatric patients N = 39		Adult patients N = 18		All patients N = 57	
	All grades 1-4	Grade 3-4 %	All grades 1-4	Grade 3-4	All grades 1-4	Grade 3-4
Biochemical parameters						
Decreased phosphate	64%	0%	56%	11%[c]	61%	3.5% [c]
Decreased calcium (corrected)	59%	0%	67%	0%	61%	0%
Increased creatinine	46%	0%	11%	0%	35%	0%
Increased glycosylated hemoglobin (HbA1C) [a]	28% [a]	N/A [a]	67% [a]	N/A [a]	40% [a]	N/A [a]
Increased glucose [b]	10%	0%	11%	6%[c]	11%	1.8%[c]

Abbreviation: N/A, not available.

[a] No CTCAE grade available. All laboratory abnormalities with HbA1C value ≥ 5.7% are shown, regardless of value at baseline.

[b] Glucose increase is an expected laboratory abnormality of PI3K inhibition.

[c] No Grade 4 laboratory abnormalities were reported.

Source: [PROS SCS Appendix 2-Table 17.2-5.4 and Table 17.3-1.6]

Adverse events of special interest-AESI

The AESI selected for alpelisib were aligned with AESI in the oncology setting and are: gastrointestinal toxicity (nausea, vomiting and diarrhea), hyperglycaemia, hypersensitivity, severe cutaneous reactions, rash, pneumonitis, and pancreatitis. Additionally, stomatitis has been considered as an AESI for alpelisib for the PROS indication.

The table 10-34 summarizes AESI by SOC and PTs reported during EPIK-P1 study:

Table 10-34 Overview of adverse events of special interest by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (<18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Safety topic PT	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
GI toxicity (Nausea Vomiting Diarrhea) (AESI)	2 (18.2)	0	3 (25.0)	0	2 (12.5)	0	7 (17.9)	0	6 (33.3)	0	13 (22.8)	0
Diarrhoea	1 (9.1)	0	3 (25.0)	0	1 (6.3)	0	5 (12.8)	0	4 (22.2)	0	9 (15.8)	0
Nausea	0	0	0	0	1 (6.3)	0	1 (2.6)	0	1 (5.6)	0	2 (3.5)	0
Vomiting	0	0	1 (8.3)	0	0	0	1 (2.6)	0	1 (5.6)	0	2 (3.5)	0
Abdominal pain	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Constipation	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Gastroenteritis	1 (9.1)	0	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Hyperglycaemia (AESI)	0	0	1 (8.3)	0	2 (12.5)	0	3 (7.7)	0	5 (27.8)	0	8 (14.0)	0
Hyperglycaemia	0	0	0	0	2 (12.5)	0	2 (5.1)	0	5 (27.8)	0	7 (12.3)	0
Ketosis	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Type 2 diabetes mellitus	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Hypersensitivity (AESI)	0	0	0	0	1 (6.3)	0	1 (2.6)	0	4 (22.2)	0	5 (8.8)	0
Eczema	0	0	0	0	1 (6.3)	0	1 (2.6)	0	3 (16.7)	0	4 (7.0)	0
Angioedema	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Vaginal ulceration	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Stomatitis (AESI)	2 (18.2)	0	3 (25.0)	0	1 (6.3)	0	6 (15.4)	0	3 (16.7)	0	9 (15.8)	0
Aphthous ulcer	1 (9.1)	0	1 (8.3)	0	1 (6.3)	0	3 (7.7)	0	3 (16.7)	0	6 (10.5)	0
Stomatitis	1 (9.1)	0	2 (16.7)	0	0	0	3 (7.7)	0	0	0	3 (5.3)	0

3.3.7.3. Serious adverse events, deaths, and other significant events

▪ Serious adverse events

The table 10-31 presents serious adverse events in paediatric and adult patients.

Table 10-31 Serious adverse events irrespective of study treatment relationship by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	3 (27.3)	1 (9.1)	2 (16.7)	0	5 (31.3)	2 (12.5)	10 (25.6)	3 (7.7)	11 (61.1)	9 (50.0)	21 (36.8)	12 (21.1)
Cellulitis	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	1 (5.6)	1 (5.6)	2 (3.5)	2 (3.5)
Dehydration	0	0	1 (8.3)	0	0	0	1 (2.6)	0	1 (5.6)	1 (5.6)	2 (3.5)	1 (1.8)
Gait disturbance	1 (9.1)	0	1 (8.3)	0	0	0	2 (5.1)	0	0	0	2 (3.5)	0
Pain in extremity	0	0	0	0	0	0	0	0	2 (11.1)	1 (5.6)	2 (3.5)	1 (1.8)
Vascular malformation	1 (9.1)	0	0	0	1 (6.3)	0	2 (5.1)	0	0	0	2 (3.5)	0
Acidosis	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Adrenal insufficiency	0	0	0	0	1 (6.3)	1 (6.3)	1 (2.6)	1 (2.6)	0	0	1 (1.8)	1 (1.8)
Back pain	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Disseminated intravascular coagulation	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Dyspnoea	1 (9.1)	1 (9.1)	0	0	0	0	1 (2.6)	1 (2.6)	0	0	1 (1.8)	1 (1.8)
Fall	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Fatigue	0	0	0	0	1 (6.3)	0	1 (2.6)	0	0	0	1 (1.8)	0
Haematoma muscle	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Hyperglycaemia	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Hypotonia	1 (9.1)	0	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Impaired healing	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Inflammation	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Influenza	0	0	0	0	1 (6.3)	0	1 (2.6)	0	0	0	1 (1.8)	0
Lethargy	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Lipoma	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Multiple fractures	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Otitis media acute	0	0	0	0	1 (6.3)	0	1 (2.6)	0	0	0	1 (1.8)	0
Pneumomediastinum	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Post procedural discomfort	1 (9.1)	0	0	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0
Pulmonary contusion	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Pulmonary embolism	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Renal impairment	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Streptococcal sepsis	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Thrombophlebitis	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Urinary tract infection	0	0	0	0	1 (6.3)	0	1 (2.6)	0	0	0	1 (1.8)	0
Vaginal haemorrhage	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Venous thrombosis limb	0	0	0	0	0	0	0	0	1 (5.6)	0	1 (1.8)	0
Volvulus	0	0	0	0	0	0	0	0	1 (5.6)	1 (5.6)	1 (1.8)	1 (1.8)
Vomiting	0	0	1 (8.3)	0	0	0	1 (2.6)	0	0	0	1 (1.8)	0

▪ No deaths were reported during EPIK-P1 study.

▪ No Drug interruptions and dose adjustments due to adverse events.

The table 10-26 summarizes data related to drug interruption and dose adjustment:

Table 10-26 Dose adjustments and discontinuation of alpelisib by age category (Full study population)

	2-5 years N=11	6-11 years N=12	12-17 years N=16	Pediatric patients (<18 years) N=39	Adult patients (≥18 years) N=18	All patients N=57
Number of patients - n (%)						
With no dose reduction and/or interruption	11 (100)	11 (91.7)	13 (81.3)	35 (89.7)	13 (72.2)	48 (84.2)
With at least one dose reduction and/or interruption	0	1 (8.3)	3 (18.8)	4 (10.3)	5 (27.8)	9 (15.8)
Dose reduction						
Number of patients - n (%)						
With no dose reduction	11 (100)	12 (100)	16 (100)	39 (100)	14 (77.8)	53 (93.0)
With at least one dose reduction	0	0	0	0	4 (22.2)	4 (7.0)
Only one dose reduction	0	0	0	0	4 (22.2)	4 (7.0)
Number of patients with at least one dose reduction by reason - n (%)						
Adverse event	0	0	0	0	2 (11.1)	2 (3.5)
Physician decision	0	0	0	0	2 (11.1)	2 (3.5)
Dose interruption						
Number of patients - n (%)						
With no dose interruption	11 (100)	11 (91.7)	13 (81.3)	35 (89.7)	13 (72.2)	48 (84.2)
With at least one dose interruption	0	1 (8.3)	3 (18.8)	4 (10.3)	5 (27.8)	9 (15.8)
Only one dose interruption	0	0	2 (12.5)	2 (5.1)	5 (27.8)	7 (12.3)
Two dose interruptions	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
More than two dose interruptions	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Number of patients with at least one dose interruption by reason - n (%)						
Adverse event	0	1 (8.3)	1 (6.3)	2 (5.1)	4 (22.2)	6 (10.5)
Physician decision	0	0	1 (6.3)	1 (2.6)	0	1 (1.8)
Subject decision	0	0	1 (6.3)	1 (2.6)	1 (5.6)	2 (3.5)
Other	0	1 (8.3)	2 (12.5)	3 (7.7)	0	3 (5.3)
Dose increase						
Number of patients - n (%)						
With no dose increase	11 (100)	7 (58.3)	11 (68.8)	29 (74.4)	18 (100)	47 (82.5)
With at least one dose increase	0	5 (41.7)	5 (31.3)	10 (25.6)	0	10 (17.5)
Only one dose increase	0	4 (33.3)	4 (25.0)	8 (20.5)	0	8 (14.0)
Two dose increases	0	1 (8.3)	1 (6.3)	2 (5.1)	0	2 (3.5)
Number of patients with at least one dose increase by reason - n (%)						
Disease improvement under study	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
Physician decision	0	2 (16.7)	5 (31.3)	7 (17.9)	0	7 (12.3)
Guardian decision	0	1 (8.3)	0	1 (2.6)	0	1 (1.8)
Other	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.
Source: Table 14.3-1.3

3.3.7.4. Laboratory findings

Haematology

The most frequently reported haematological abnormalities were:

▪ decreased leukocytes, all 38.6% (n=17): 43.6% (n=11) in paediatric population and 27.8% (n=5) in adult patients.

▪ increased lymphocytes, 24.6% (n=14): 33.3% (n=13) in paediatric population and 5.6% (n=1) in adult patients.

▪ decreased lymphocytes, 21.1% (n=12), 28.2% (n=11) in paediatric population and 5.6% (n=1) in adult patients.

▪ decreased haemoglobin, all 33.3% (n=19 patients): 35.9% (n=14) in paediatric population and 27.8% (n=5) in adult patients.

▪ decreased platelets (12 patients, 21.1%): 17.9% (n=7) in paediatric population and 27.8% (n=5) in adult patients.

▪ decreased neutrophils (10 patients, 17.5%): 23.1% (n=9) in paediatric population and 5.6% (n=1) in adult patients.

There were mostly grade 1 and grade 2. The grade 3 abnormalities reported were:

- Decreased haemoglobin: 5.3% (n=3, 2 paediatric and 1 adult)
- Increased leukocytes: 1.8% (n=1 paediatric patient)
- Decreased lymphocytes: 1.8% (n=1 adult patient)
- Decreased neutrophils: 1.8% (n=1 adult patient)
- Decreased platelets: 1.8% (n=1 adult patient)

No grade 4 events were reported.

Clinical chemistry

The main laboratory abnormalities reported during EPIK-P1 study and were mostly grade 1 or 2:

▪ Blood calcium decreased, all patients 61%: 59% paediatric patients and 56% adult patients. No grade 3 or higher.

▪ Blood phosphorus decreased, all patients 61%: 64% paediatric patients and 56% adult patients. No grade 3 or higher in paediatric patients but 11% of adult patients had Grade 3 or higher (see below).

▪ Blood creatinine increased, all patients 35%: 46% paediatric patients and 11% adult patients. No grade 3 or higher.

▪ Glycosylated haemoglobin increased all patients 40%: 28% paediatric patients and 67% adult patients.

▪ Glucose increased, all patients 11%: 10% paediatric patients and 11% adult patients. No grade 3 or higher in paediatric patients but 6% of adult patients had Grade 3 or higher AE of glucose increased (see below).

The following grade 3 biochemistry abnormalities were reported:

- Increased bilirubin: two patients, 3.5%: both were adults
- Decreased phosphate: two patients, 3.5%: both were adults
- Increased glucose: one patient, 1.8%: adult patient
- Increased magnesium: one patient, 1.8%: paediatric patient
- Decreased sodium: one patient, 1.8%: adult patient

The following grade 4 biochemistry abnormalities were reported (as explained above):

- Increased urate: two patients, 3.5%: one paediatric and one adult

- Decreased magnesium: one patient, 1.8%: adult patient

3.3.7.5. In vitro biomarker test for patient selection for safety

N/A.

3.3.7.6. Safety in special populations

▪ Intrinsic factors

For the safety assessment, impact of age on the AE profile of alpelisib in PROS patients was assessed across the following age categories: 2-5 years; 6-11 years; 12-17 years; paediatric patients (2-17 years); and adult patients (≥ 18 years). Based on the available data, no safety issues have been identified from the gender, race, ethnicity and BMI of patients.

No dose adjustment is needed in patients with mild or moderate renal impairment whilst caution is recommended in patients with severe renal impairment due to the lack of experience in this population.

No dose adjustment is needed in patients with mild, moderate and severe hepatic impairment.

▪ Extrinsic factors

Safety in special population

No safety issues related to age, sex, race, BMI, ethnicity/region has been identified.

Pregnancy, reproduction 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. A mechanistic rationale (PI3 kinase inhibitors) suggests reproductive and developmental toxicity.

Overdose and drug abuse: No safety issues have been identified related to overdose, drug abuse and effect of alpelisib on mental concentration.

Withdrawal and rebound

No safety issues have been identified related to withdrawal and rebound with alpelisib in PROS patients during EPIK-P1 study.

Effect on ability to drive or operate machinery or impairment of mental ability

No new information has been generated in support of this application. No studies have been performed to evaluate the effects of alpelisib on the ability to drive or operate machinery, or the impairment of mental ability.

3.3.7.7. Immunological events

No antidrug antibodies were identified with alpelisib.

3.3.7.8. Safety related to drug-drug interactions and other interactions

No new data on drug interactions were generated in EPIK-P1.

3.3.7.9. Discontinuation due to adverse events

None of the patients discontinued study treatment due to AEs during EPIK-P1 study.

3.3.7.10. Post marketing experience

The assessment of the third PSUR (EMEA/H/C/PSUSA/00010871/202111) led to amend the section 4.2, 4.4 and 4.8 of Piqray SmPC adding mentions related to the risks of colitis and angioedema. The proposed SmPC for Vijoice adequately reflects these changes. Moreover, according to the PRAC "Other considerations", the results of the DDI study CBYL719A2110 and the proposed SmPC updates (section 4.5 and 5.2) had been submitted in a separate procedure (EMEA/H/C/004804/II/0012) as well as the results of the fertility studies (study 2070119 and study 2070120) and SmPC updates (section 4.6 and 5.3) accordingly (EMEA/H/C/004804/II/0013).

3.3.8. Discussion on clinical safety

During EPIK-P1 study, regardless study treatment relationship, at least one adverse event was experienced by 82.5% (n=47) of overall patients: 79.5% (n=31) in paediatric patients and 88.9% (n=16) in adult patients.

▪ In paediatric patients, the most frequently (>10%) affected SOCs were: gastrointestinal disorders (30.8%, n=12), general disorders and administration site conditions (23.1%, n=9), infections and infestations (23.1%, n=9), metabolism and nutrition disorders (15.4%), nervous system disorders (12.8%), blood and lymphatic system disorders (10.3%) and respiratory, thoracic and mediastinal disorders (10.3%).

AEs reported in ≥ 5% of paediatric patients were diarrhea (12.8%), vascular malformation (10.3%), aphthous ulcer (7.7%), inflammation (7.7%), hypoglycaemia (7.7%), pain in extremity (7.7%), hyperglycaemia (5.1%), and gait disturbance (5.1%).

In the paediatric subcategories, the most frequently (≥ 5%) observed AEs were:

- 2-5 years age group: inflammation (18.2%), diarrhoea (9.1%), gait disturbance (9.1%), dyspnoea (9.1%), hypoglycaemia (9.1%) and pain in extremity (9.1%).

- 6-11 years age group: diarrhoea (25.0%, n=3), stomatitis (16.7%), vascular malformation (8.3%), dehydration (8.3%), aphthous ulcer (8.3%), disseminated intravascular coagulation (8.3%).

- 12-17 years age group: hyperglycaemia (12.5%), vascular malformation (12.5%), hypoglycaemia (12.5%), diarrhoea (6.3%), aphthous ulcer (6.3%), disseminated intravascular coagulation (6.3%), inflammation (6.3%), dry skin (6.3%), eczema (6.3%), cellulitis (6.3%), pain in extremity (6.3%), adrenal insufficiency (6.3%) and wound infection (6.3%).

▪ In adult patients, the most frequently (>10%) affected SOCs were: skin and subcutaneous disorders (55.5%, n= 10), gastrointestinal disorders (44.4%, n=8), metabolism and nutrition disorders (33.3%, n=6), nervous system disorders (27.8%, n=5), musculoskeletal and connective tissue disorders (27.8%, n=5), vascular disorders (27.8%, n=5), reproductive system and breast disorders (27.8%, n=5), general disorders and administration site conditions (22.2%, n=4), infections and infestations (22.2%, n=4), blood and lymphatic system disorders (22.2%, n=4) and respiratory, thoracic and mediastinal disorders (16.7%, n=3), endocrine disorders and injury (11.1%, n=2), poisoning and procedural complications (11.1%, n=2).

AEs reported in ≥ 5% of adults patients were hyperglycaemia (27.8%), diarrhoea (22.2%), vascular malformation (10.3%), aphthous ulcer (16.7%), disseminated intravascular coagulation (16.7%), dry skin (16.7%), eczema (16.7%), alopecia (16.7%), headache (16.7%), inflammation (11.7%), cellulitis

(11.1%), pain in extremity (11.1%), hypoglycaemia (7.7%). Gait disturbance, dehydration, fall, impaired healing, multiple fractures, pulmonary embolism, renal impairment, streptococcal sepsis, vaginal haemorrhage, volvulus, wound infection (5.6% each).

Some adverse events only occurred in adult patients such as alopecia and headache whilst vascular malformation, stomatitis and hypoglycaemia only occurred in paediatric patients.

Most of AEs were grade 1 or 2 but 22.8% were grade 3 or higher. These events were generally explained by underlying conditions related to PROS (e.g. disseminated intravascular coagulation, inflammation, cellulitis, pain in extremity, renal impairment) or by coincidental events (e.g. fall, multiple fractures, streptococcal sepsis subsequent to a serious car accident).

Cellulitis was the most frequently reported grade 3/4 AE and occurred in two patients (3.5%): one in paediatric population and one in adult population. Cellulitis is further discussed thereafter.

One adult patient reported a grade 4 event of pulmonary embolism which may have been a pre-existing condition as such, relationship with study drug was entered as not applicable However, due to partial start and end date available, this event was considered to be treatment emergent due to imputation rules applied by the applicant.

Overall, these adverse events are consistent with the mechanism of action and the known safety profile of alpelisib in breast cancer indications.

Treatment related AEs

▪ Treatment-related AEs were reported in 23.1% paediatric patients (n=9) and the main reported events, ≥ 5%, were aphthous ulcer, stomatitis (7.7%, n=3 each), and hyperglycaemia (5.1%, n=2). No paediatric patient had treatment-related grade 3 or higher AEs. Overall, there was no meaningful difference observed in the safety profile across various age groups within the paediatric patients.

▪ Treatment-related AEs were reported in 13 adult patients (72.2%) and TRAEs reported in ≥ 5% patients were hyperglycaemia (27.8%, n=5), aphthous ulcer and alopecia (16.7% n=3 each), and cellulitis (5.6%, n=1) (see also section 4.3.4 Adverse events of special interest).

No grade 4 treatment-related AEs were reported in both population of patients.

Adverse Events of Special Interest (AESI)

◇ *Gastro-intestinal toxicity: nausea, vomiting and diarrhea*

Gastrointestinal AESIs, nausea, vomiting and diarrhea were reported in 13 patients (22.8%). The most common AE was diarrhea, 15.8% (n=9). Nausea and vomiting occurred in two patients (3.5% each). These AEs were grade 1 or 2.

Treatment-related AEs of diarrhea and nausea were reported in one adult patient each (1.8%). A single SAE of vomiting was reported (one patient, 1.8%). Vomiting in two patients (3.5%) and nausea in one patient (1.8%) led to dose interruption.

The assessment of the corresponding narratives cannot allow to clearly establish any causal association with alpelisib but to consider it as possible due to the compatible TTO. However according to the 3rd PSUSA for alpelisib in the treatment of locally advanced or metastatic breast cancer, nausea, vomiting and diarrhoea belong to the list of adverse reactions that were the most reported and known as very common AEs when alpelisib is administered either as a single agent or in combination. Due to the deleterious clinical consequences (dehydration, acute kidney injury), diarrhea, nausea and vomiting are

listed in section 4.8 of the proposed SmPC. Additional warning and recommendations are also proposed as well and supported by the Rapporteur.

In respect to the risk of colitis, cases were reported during treatment with alpelisib in the oncology setting and this has been the subject of a signal assessed as part of the last PSUSA leading to update Piqray® SmPC. Even though no colitis were reported during EPIK-P1 study, colitis may occur in PROS patients treated with alpelisib and then colitis has been added in the section 4.2 and 4.4 of the proposed SmPC. This is endorsed.

Treatment-related adverse events of stomatitis, aphthous ulcer and dry mouth were also reported in 5.3%, 10.5% and 1.8% patients, respectively (see also thereafter part on "Stomatitis").

◇ *Hyperglycaemia*

Fourteen percent (14%, n=8) of the overall patient populations experienced hyperglycaemia. The median duration of exposure to alpelisib was 27.2 months (range: 9.9-49.9).

In paediatric patients, hyperglycaemia were reported in 5.1% (n=2) and ketosis in 2.6% (n=1)).

No grade 3/4 AEs were reported. All events of hyperglycaemia were assessed as treatment related. No SAEs were reported and none of the AEs led to dose interruption.

In adult patients, hyperglycaemia AESIs were reported for five adult patients (27.8%), including the PTs of hyperglycaemia in five patients (27.8%) and type 2 diabetes mellitus in one patient (5.6%). These AEs were all low grade (grade 1 and 2). A single SAE was reported (one patient, 5.6%) and none of the AEs led to dose interruption or reduction. The majority of events were resolved without change of alpelisib dose (no dose adjustment or corrective treatment). Three adult patients started anti-diabetic treatment.

Two adverse events of hyperglycaemia (grade 1 and 2, respectively) and Type 2 diabetes mellitus (grade 2) were reported in patient. On Day 435, the patient developed transient hyperglycaemia (grade 1) which was resolved on the same day, without any action taken with alpelisib. The patient had chronic kidney dysfunction and was pre-diabetic at index date (HbA1c was 5.7%). The patient had several urinary tract infections because of the underlying paraplegia and during one of them (Day 1004) the patient developed hyperglycaemia along with dehydration, acute and transient renal dysfunction requiring hospitalization. After 6 days, all events resolved, and the patient was discharged. No action was taken with alpelisib. These events were confounded by underlying conditions of urinary tract infection and severe chronic kidney disease as reported by the physician.

For the two adult patients who experienced increase in plasma glucose consistent with the Common Toxicity Criteria grade ≥ 2 event (based on laboratory data), the time to first occurrence was 81 days and 134 days, respectively.

Several hyperglycaemias related to alpelisib have been observed in cancer patients, more frequently in patients who are diabetic. Therefore, such events were expected in PROS patients. The risk of hyperglycaemia and blood glucose increase are listed in the proposed SmPC as well as a warning in the 4.4 section. Only one patient experienced ketoacidosis but no clear relationship with alpelisib can be made at this stage. Since adverse reactions of ketoacidosis occurred in cancer patients, one cannot ruled out them in PROS patients. Ketoacidosis should be closely monitored as part of the forthcoming PSUR.

Table 10-33 Adverse events requiring additional therapy (any grade morethan 5% or reported by at least one patient as grade 3 or higher in the overall population) irrespective of study treatment relationship by preferred term and age category (Full study population)

	2-5 years N=11		6-11 years N=12		12-17 years N=16		Pediatric patients (< 18 years) N=39		Adult patients (≥18 years) N=18		All patients N=57	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	4 (36.4)	1 (9.1)	2 (16.7)	0	9 (56.3)	2 (12.5)	15 (38.5)	3 (7.7)	15 (83.3)	9 (50.0)	30 (52.6)	12 (21.1)
Hyperglycaemia	0	0	0	0	2 (12.5)	0	2 (5.1)	0	3 (16.7)	0	5 (8.8)	0

◇ *Hypersensitivity*

Five patients (8.8%) experienced hypersensitivity AEs. These events were all grade 1 or 2. No grade 3/4 AEs were reported. The PTs of eczema was reported in four patients (7%), angioedema, and vaginal ulceration were reported in one patient each (1.8%). None of the AEs reported required dose modifications of alpelisib, and were manageable with appropriate concomitant medication if any. Although these cases cannot allow a proper causality assessment of alpelisib due to confounding factors or limited information, hypersensitivity reactions were commonly reported during the pivotal trials for breast cancer indication where the number of patients was almost 5-fold higher than in EPIK-P1 study.. The Applicant did not consider the risk of hypersensitivity for the section 4.8 of Vijoice since this has been experienced in oncology patients and no case reported during the clinical trials in PROS patients. The Rapporteur agrees that a warning in the section 4.4 may appear sufficient at this stage. However, considering the seriousness of hypersensitivity reactions, that may be life-threatening, and that such an ADR was commonly reported during clinical trials in oncology patients, the Applicant should discuss the mention of this risk in the safety concerns of the RMP as an important potential risk **(LoOI)**.

◇ *Pneumonitis*

Because pneumonitis was reported during studies X2101, X1101 and SOLAR-1 performed in patients with malignancies, this has been considered as an AESI by the applicant. In X2101 and X1101 studies, two patients experienced pneumonitis but they were considered related to alpelisib only in study X1101. Pneumonitis was grade 1 in one patient and grade 2 in the other. The grade 2 event was a SAE, and study drug was interrupted due to the event. In SOLAR-1 study, pneumonitis events occurred in 5 patients in the alpelisib plus fulvestrant treatment arm and in 1 patient in the placebo plus fulvestrant treatment arm. All of these events were considered treatment-related by the investigator. One patient had a grade 3 event in the alpelisib plus fulvestrant treatment arm. There were no grade 4 events. Treatment with alpelisib was discontinued in 4 patients.

Pneumonitis is listed in the section 4.8 of Piqray SmPC as a common adverse reaction and is considered an important identified risk as per the Piqray EU RMP.

Based on the clinical experience in the oncology setting, pneumonitis are mentioned as an important identified risks in the RMP of alpelisib in PROS patients. A warning is also stated under the section 4.4 of the proposed SmPC. This is endorsed by the Rapporteur.

◇ *Pancreatitis*

Pancreatitis were reported in SOLAR- study in 23 patients in the alpelisib plus fulvestrant treatment arm and only one was considered as related to the study treatment. It was a grade 4 AE and the patient was discontinued from study treatment and recovered from this event after discontinuation. In the study X1101 and X2101, there was no diagnosis of pancreatitis but lipase and amylase increased.

Pancreatitis is listed in the section 4.8 of Piqray SmPC as an uncommon adverse reaction but has not been identified as a safety concerns as per the Piqray EU RMP.

Considering the low frequency of pancreatitis observed in cancer patients, no further pharmacovigilance activities are requested in PROS patients. Safety data from ongoing long-term studies and forthcoming PSUR will provide further information on this risk.

◇ *Rash*

No rash has been reported in EPIK-P1.

Twenty-four (24) adverse events related to rash have been reported in 18 PROS who received alpelisib in the compassionate use programs outside of EPIK-P1 (CBYL719F12001M, CBYL719XFR01I and CBYL719X2001I, cut-off date 28-Feb-2022). Thirteen events were rash, 3 were rash pruritic, 3 were rash erythematous, 2 were rash maculopapular, 2 were rash popular and one was dermatitis acneiform. Three SAEs were reported, including two cases in which rash was reported as a symptom of cellulitis and causality was not suspected. Of the 18 patients, seven were paediatric patients: 5 patients received 50 mg and two adolescent patients received 100 mg alpelisib daily. The investigators suspected a causal relationship with alpelisib in 11 out 18 patients. Furthermore, non-serious pruritus was reported in 6 patients, including 4 paediatric patients and the majority (5 out 6) were reported with suspected causality.

The applicant concludes that since skin reactions such as rash and pruritus are a class-effect of PI3K/mTOR inhibitors and have been commonly observed with alpelisib in the oncology setting, these terms are proposed for inclusion in the PROS SmPC as events reported in compassionate use programs outside of EPIK-P1. The applicant conclusion and proposal are supported by the Rapporteur.

◇ *Severe cutaneous adverse reaction*

Severe cutaneous reaction occurred in 3 patients receiving single-agent alpelisib in Study X2101 (two at the 400 mg dose, and one at the 450 mg dose).The AE were a dermatitis exfoliative (grade 3), an erythema multiform (grade 2) and one exfoliative rash (grade 1). Erythema multiforme was a serious AE which required hospitalization and led to interruption of the study drug.

In SOLAR-1, 4 patients experienced severe cutaneous reactions in the alpelisib plus fulvestrant treatment arm (all considered treatment-related) whilst no event in the placebo arm. The AEs corresponded to the following PT: 3 AE of erythema multiform (one grade 2 and 2 grade 3) and one patient experienced a grade 3 Stevens-Johnson syndrome (SJS).

No severe cutaneous reactions were reported during the study X1101.

Sever cutaneous adverse reactions is considered an important identified risk as per the Piqray EU RMP. Erythema multiforme, DRESS, and Stevens-Johnson syndrome are adverse reactions listed in the current Piqray SmPC.

Based on the clinical experience in the oncology setting, severe cutaneous reactions are mentioned as an important identified risks in the RMP of alpelisib in PROS patients. A warning is also stated under the section 4.4 of the proposed SmPC. This is endorsed by the Rapporteur.

◇ *Stomatitis*

The adverse event of stomatitis included stomatitis and aphthous ulcer.

In paediatric patients: 15.4% (n=6) paediatric patients experienced stomatitis. Aphthous ulcer and stomatitis were reported in 3 (7.7%) patients each. All were grade 1 in severity.

In Adult patients: 16.7% (n=3) adult patients experienced stomatitis, all corresponding to aphthous ulcer. Two events were grade 1 and one was grade 2.

Whilst the causality of alpelisib in the occurrence of aphthous ulcer is supported, as regards the 3 specific events of stomatitis which occurred in paediatric population, the assessment of the corresponding narratives cannot allow any causal association with alpelisib to be established. Indeed, even though the time-to-onset is compatible with alpelisib treatment, the event disappears without any particular action: alpelisib was pursued or even the dose increased. For one patient, the event appears a long time after the initiation of alpelisib and disappeared the same day.

The assessment of adverse events of special interest with alpelisib is consistent with its mechanism of action as well as its safety profile in the oncology indications. Hence, for gastro-intestinal toxicity (nausea, vomiting and diarrhoea), hyperglycaemia, hypersensitivity, rash and stomatitis related adverse events they are listed in the proposed SmPC for PROS indication.

Even though no AESI of pneumonitis and sever cutaneous adverse reactions were observed during EPIK-P1 study and as part of the compassionate use of alpelisib in PROS patients, they have been considered by the applicant as AESI in PROS patient with a statement in the SmPC and in the RMP as important identified risks.

Besides the appraisal of the applicant data raises the following concerns:

- The AE of headache is listed as a common adverse reaction. Three patients experienced headache all in the adult population.

- Thrombophlebitis was experienced in one patient. But no causal association with alpelisib can be established.

Furthermore, osteonecrosis of jaw (ONJ) was reported in cancer patients during combination with bisphosphonates or RANK-ligand inhibitors. Since, bisphosphonate can be indicated for treatment of osteoporosis, then out of the oncology field, one cannot exclude that PROS adult patients received both treatments. Cumulatively, the Applicant reports 30 cases of ONJ from the last PSUR 5, (Data Lock Point (DLP) 23-Nov-2022). But the Applicant considers that such risk is not applicable to the PROS population, which consists primarily of paediatric patients and young adults who are far less likely to receive concomitant treatments associated with a risk of osteoporosis. According to demographic data from EPIK-P1 and EPIK-P2 studies, it is agreed that most of the patients were paediatric patients (39 patients 68.4%) but 18 patients were adult patient with a range from 18 to 50 years. The safety profile of alpelisib should be assessed for all age categories of patients, taking into account their specificities and regardless the number of patient exposed at a given time. Hence since alpelisib is intended to be used in adult patient without limit of age, even though no event of osteonecrosis of jaw have occurred during clinical studies, one cannot discard such risk in adult patient as part of post-marketing experience. Therefore, the seriousness and the disability that osteonecrosis of the jaw can induce invite to consider this risk for the safety concerns of the RMP as an important potential risk based on the clinical experience with alpelisib in oncology patients **(see LoI RMP part).**

Serious adverse events

Overall, more than one-third of patients (36.8%, n=21) experienced a serious adverse event. Grade 3 or higher occurred in 21.1% patients (n=12). The main preferred terms were cellulitis (3.5%, n=2), dehydration, pain in extremity, adrenal insufficiency, disseminated intravascular coagulation, dyspnoea, fall, impaired healing, inflammation, multiple fractures, pulmonary embolism, renal impairment, streptococcal sepsis, vaginal haemorrhage, and volvulus (1.8% each, n=1). Only one grade 4 SAE of pulmonary embolism was reported.

In paediatric patients, SAEs occurred in 25.6% patients (n=10) and grade 3 SAEs occurred in 7.7% (n=3). None of the paediatric patients reported grade 4 SAE. No treatment-related SAEs were observed in paediatric patients.

In adult patient, 61.1% (n=11) adult patients experienced SAEs and 9 patients had Grade 3 or higher SAEs. Treatment-related SAEs (all grades) included cellulitis, hyperglycaemia and venous thrombosis limb in one patient each.

The adverse events of a pulmonary embolism and disseminated coagulation intravascular were analysed and the assessment of their corresponding narratives cannot allow a causal association with alpelisib to be established.

Deaths*:* None of the patients died during the study EPIK-P1.

Discontinuations: None of the patients discontinued study treatment due to AEs during EPIK-P1 study.

Interruptions and doses reductions: At least one dose interruption, regardless the reasons, was made in 15.8% (n=9) of the overall patients: 10.3% (n=4) in paediatric patients and 27.8% (n=5) in adult patients. Dose interruptions due to AEs were actually 10.5% (n=6): 5.1% (n=2) in paediatric patients and 22.2% (n=4) in adult patients. Other drug interruptions were due to physician decision (1.8%, n=1), subject decision (3.5%, n=2), and 'other' (5.3%, n=3). The category 'other' included interruption due to surgical procedure (5.1%, n=2) and, in one case the patient forgot medication.

No dose reduction were reported in paediatric patients whilst 22.2% (n=4) of adult patients required at least one dose reduction. AEs related dose reductions were alopecia memory impairment, multiple inflammatory episodes, cystitis, dizziness, nausea, headaches.

Laboratory findings

Hematology

The haematological abnormalities occurred after the introduction of alpelisib. The applicant claims that these events were generally consisted of transient shifts followed by returns to normal values with no alpelisib dose modification and none of the abnormalities were considered clinically significant. Most of them could be explained by underlying or concurrent medical conditions.

Blood and lymphatic system disorders have been reported in the oncology setting such as anaemia, lymphocyte count decreased and platelet count decreased. However, no signals of haematological abnormalities has been identified at this stage in PROS patient.

Clinical chemistry

The main laboratory abnormalities reported during EPIK-P1 study were mostly grade 1 or 2. Two patients experienced reported increased urate: one in adult patient due to a system error of data entry and one in paediatric patient who had existing grade 4 increased urate at baseline.

Most of the events related to chemistry were also reported in cancer patients and listed in section 4.8 of Piqray SmPC except blood phosphorus decreased which occurred in PROS patients.

No hypokalaemia were observed as well as no patient had alanine aminotransferase (ALT), aspartate aminotransferase (AST) elevations >3xULN (grade 2 or higher), or gamma-glutamyl transferase (GGT) increased.

The applicant listed blood calcium decreased, blood phosphorus decreased, blood creatinine increased, glycosylated haemoglobin increased and glucose increased under the section 4.8.

Other parameters: Growth and development of paediatric patients in EPIK-P1

The effects of alpelisib on growth and development are missing information in the safety concerns of the Risk Management Plan. The Applicant has detailed how that will be applied the monitoring of growth, bone/dental development and sexual maturation during the long-term study EPIK-P2. Assessments will be performed locally in appropriate groups at screening, every 6 months and at the End of Treatment visit. Bone development assessments may be stopped when participant reaches skeletal maturity or Tanner stage 5. All findings will be recorded and assessed for clinical significance, and clinically significant abnormalities will be reported as adverse events. If clinically significant changes in growth, bone/dental development, and sexual maturation are observed, the Investigator should reassess the risk/benefit ratio of continued alpelisib treatment and discuss with the Sponsor on a case-by-case basis. Additionally, blood phosphate and calcium levels will be collected as part of the chemistry test category of the laboratory parameters collection plan included in this study.

However, the long-term safety, notably effects on growth and development in the paediatric population, remains uncertain (presently data in cancer patient cannot allow any response to be given). No prospective, long-term, mature data are currently available, and they are not expected until 2028, at the earliest. The Applicant is proposing to list this concern as missing information in the RMP. This concern, in addition to the uncertainties previously identified regarding long-term data should be taken into consideration in the assessment of the benefit-risk balance of the requested indication **(see remaining LoI, MO).**

Vital signs and ECG findings

No clinically significant findings were observed based on the evaluation of systolic and diastolic blood pressure, pulse rate, weight, and height among paediatric patients and adult patients

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

Besides, the assessment of the 3 PSURs and also safety data from EPIK-P1 have not revealed any signal of cardiac arrhythmias-related to adverse events

Safety in special population

No safety issues related to age, sex, race, BMI, ethnicity/region has been identified.

Pregnancy

There were no pregnancies events reported in the alpelisib clinical development program. Pregnant women were excluded in anticipation of a possible teratogenic effect.

Studies in animals have shown reproductive toxicity (embryotoxic, foetotoxic and teratogenic). A mechanistic rationale for the reproductive and developmental toxicity may be explained by: The role of PI3K in angiogenesis, via inhibition of VEGF signalling, a process fundamental to foetal development (1); Embryonic toxicity and malformations were induced at dose and exposure levels where insulin resistance and hyperglycemia was demonstrated or can be assumed from other studies (2); Alpelisib, like other PI3 kinase inhibitors, exerts a general inhibitory effect on proliferation of a variety of tissues, as e.g. shown in repeated-dose toxicity studies (3). All those effects are associated with the pharmacological activity of alpelisib and were observed at pharmacologically active exposure levels.

Alpelisib and its main metabolite BZG791 is considered free of a genotoxic potential.

Vijoice should not be used during pregnancy unless the clinical condition of the woman requires treatment with alpelisib. As a corollary, a contraindication of use Vijoice during pregnancy is not warranted.

Based on the potential risk of treatment by alpelisib and context of the disease (rare and severe nature of the disease), the probability of pregnancy initiation in this context is low and a pregnancy test at initiation of treatment in a woman of childbearing potential is relevant.

Based on Vijoice can cause foetal harm when administered to a pregnant woman and the elimination half-life of alpelisib (8 to 9 hours), advise women of childbearing potential to use effective contraception during treatment with Vijoice and for 1 week after the last dose is appropriate.

The reported margin of exposure of 1.5-fold (between the NOAEL in the rat fertility study and assumed female exposure via an alpelisib-exposed male partner) is insufficient to exclude a potential risk of alpelisib taken by the male patient to the pregnancy outcome of his female partner. Therefore, as a precautionary measure, male patients with sexual partners who are pregnant, likely to become pregnant or who could become pregnant should use condoms during sexual intercourse while taking Vijoice and for at least 1 week after stopping Vijoice.

Lactation

Breastfeeding women were excluded of the alpelisib clinical development program and there were no breastfeeding related events were reported. There are no data on the presence of alpelisib in human milk, its effects on milk production, or the breastfed child.

Fertility

The applicant states that alpelisib may impair fertility in males and females of reproductive potential. However, in study 2070119 ("BYL719: Oral (Gavage) Study of Fertility in the Male Rat"), male fertility and reproductive performance were unaffected up to and including 20 mg/kg/day (approximately 2 times the estimated exposure [AUC] in humans at the recommended dose of 250 mg). Therefore, a more thorough discussion of the relevance in humans of the results observed in the fertility study in male rats is deemed necessary. Please note that sections 4.6 and 5.3 of the SmPC would need to be amended accordingly **(NC OC)**.

Overdose and drug abuse: No safety issues have been identified related to overdose, drug abuse and effect of alpelisib on mental concentration.

Withdrawal and rebound

No safety issues have been identified related to withdrawal and rebound with alpelisib in PROS patients during EPIK-P1 study.

Effect on ability to drive or operate machinery or impairment of mental ability

Although alpelisib has minor influence on the ability to drive and use machines, cautions are advised in the SmPC when driving or using machines, due to fatigue or blurred vision during treatment.

Fatigue was reported in 2 paediatric patients whilst no event of blurred vision.

As part of EPIK-P1 study, 2 patients reported dizziness of whom one with a compelling clinical picture since the patient experienced dizziness with a positive dechallenge and rechallenge. Further to the OC raised as regards the relevance of this case, and according to the applicant's response, an update of the proposed mention under section 4.7 adding dizziness would be warranted.

Safety related to drug-drug interactions

The DDI profile of alpelisib has been thoroughly discussed as part of the MAA of alpelisib for the treatment of breast cancer. A summary is presented in the section 2.1.10 "Pharmacokinetics interaction studies".

Of note, as a post-marketing measure (EMEA/H/C/004804/II/0012), a recent DDI study BYL719A2110 on the combination of alpelisib with rifampicin a strong inducer was assessed. The results demonstrated

that a concurrent use of strong CYP3A4 inducers markedly reduced alpelisib exposure and thus may limit the clinical efficacy of alpelisib. Hence, the co-administration of strong CYP3A4 inducers with alpelisib should be avoided. Nonetheless, the role of metabolic pathways is not fully clarified in paediatric patients with PROS due to the uncertainties regarding the exposure achieved in this subgroup of patients. Since no similarity in exposure has been demonstrated either *in silico* or *in vivo*, no similar DDI profile of alpelisib as victim or inducer can be assumed. Besides the section 4.5 of the SmPC has been updated adding a statement regarding the lack of DDI studies in paediatric patients.

3.3.9. Conclusions on clinical 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. 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 appears manageable in the clinical setting.

Even though no adverse events of pneumonitis and sever cutaneous adverse reactions were observed in PROS patient, a warning is stated in the SmPC and both are considered as important potential risks in the safety concerns of the Risk Management Plan.

However, the long-term safety, notably effects on growth and development in the paediatric population, remains uncertain (presently data in cancer patient cannot allow any response to be given). No prospective, long-term, mature data are currently available, and they are not expected until 2028, at the earliest. The Applicant is proposing to list this concern as missing information in the RMP. This concern should be taken into consideration in the assessment of the benefit-risk balance of the requested indication **(see LoI, MO).**

Additional expert consultation

Assessment of paediatric data on clinical safety

Additional safety data needed in the context of a conditional MA <under exceptional circumstances

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns (RMP version number 1.1)

Important identified risks	Hyperglycaemia
Important potential risks	Severe cutaneous adverse reactions Pneumonitis Reproductive toxicity, including impaired fertility
Missing information	Safety with long-term use, including effects on growth and development

Initially, based on the safety profile of Piqray, the Applicant proposed severe cutaneous reactions and pneumonitis to be included as important identified risks in the summary of safety concerns of Vijoice. The Applicant has also aligned the EU RMP with the Summary of Product Characteristics (SmPC). However, the assessment of safety data in PROS patients lead to reconsider this categorization. Hence the EU RMP version 1.1 has been updated to reflect the recategorization of SCARs and pneumonitis as important potential risks. This change has no impact on the SmPC, which addresses SCARs and pneumonitis in sections 4.2 and 4.4 as originally proposed.

Furthermore, within the RMP of Piqray osteonecrosis of the jaw is included as an important identified risk while it is not proposed to be included in the summary of safety concerns of Vijoice. Osteonecrosis of jaw was reported in cancer patients during combination with bisphosphonates or RANK-ligand inhibitors. Since, bisphosphonate can be indicated for treatment of osteoporosis outside of the oncology field, one cannot excluded that PROS adult patients received both treatments. The Applicant considers that ONJ does not meet the criteria for the definition of an important identified risk as per Good Pharmacovigilance Practices (GVP) annex1 Definition (Rev4) and consequently does not propose to include ONJ in the Risk Management Plan (RMP). No adverse event of ONJ occurred during clinical trials in PROS patients and then this risk does not meet the criteria of an important identified risk. Nonetheless, the seriousness of ONJ and the disability that it can induce invite to consider this risk for the safety concerns of the RMP as an important potential risk based on the clinical experience with alpelisib in oncology patients. Risk of ONJ meets the criteria for such a risk (see details in the clinical D150 AR). Therefore the Applicant is requested to add risk of osteonecrosis of the jaw in the safety concerns of the RMP as an important potential risk **(LoOI).**

3.4.1.1. Discussion on safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

- **Reproductive toxicity, including impaired fertility**

The non-clinical data demonstrate that alpelisib is embryotoxic, foetotoxic and teratogenic. In addition, animal data show that alpelisib may impair fertility in males and females of reproductive potential. Secondly, a mechanistic rationale for the reproductive and developmental toxicity may be explained by the role of PI3K in angiogenesis, via inhibition of VEGF signalling, a process fundamental to foetal development and (1); Embryonic toxicity and malformations were induced at dose and exposure levels where insulin resistance and hyperglycemia was demonstrated or can be assumed from other studies (2); Alpelisib, like other PI3 kinase inhibitors, exerts a general inhibitory effect on proliferation of a variety of tissues, as e.g. shown in repeated-dose toxicity studies (3). All those effects are associated with the pharmacological activity of alpelisib and were observed at pharmacologically active exposure levels. Thirdly, there no clinical experiences of alpelisib use during pregnancy or the potential consequence on Human fertility. Based on these elements, the inclusion of a risk: "Reproductive toxicity, including impaired fertility" as safety concern (Important Potential Risk) in the RMP is appropriate.

3.4.2. Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
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 Safety with long-term use, including effects on growth and development	Final clinical study report submission	30-Sep-2030
CBYL719F12401 (EPIK-P3): 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). 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-	Hyperglycaemia Safety with long-term use, including effects on growth and development	Final clinical study report submission	30-Sep-2028

CBYL719F12201 (EPIK-P2) summary

Study short name and title:

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).

Rationale and study objectives:

This is the first prospective study of alpelisib in participants with PROS. This study is designed to demonstrate the efficacy and assess safety and tolerability of oral daily alpelisib in participants with PROS. Both pediatric and adult participants will be enrolled, as the disease may be diagnosed at different time points during a patient's life.

Primary objective: To demonstrate the efficacy of alpelisib as measured by the proportion of participants randomized to alpelisib with a response at Week 24 in at least one of the following groups:

Group 1 (≥18 year-old)

Group 2 (6 - 17 year-old)

Key secondary objective: To demonstrate the efficacy of alpelisib vs placebo based on the comparison of the proportion of participants with response at Week 16 in Group 1 or Group 2.

Other secondary objectives:

To assess safety and tolerability of alpelisib as compared to placebo in Groups 1 and 2 up to week 16.

To assess the overall safety and tolerability of alpelisib in participants with PROS over time.

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 pediatric and adult populations.

To assess changes in target and non-target lesions over time and appearance of new lesions on treatment from baseline over time.

To assess the pharmacokinetics of alpelisib in adult and pediatric patients with PROS.

To assess changes in patient-reported pain, health-related quality of life and overall impression of symptoms in pediatric and adult populations over time.

To assess the duration of response in participants who receive 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 and thereafter every 6 months).

To assess the proportion of participants with a response at the scheduled protocol visits for disease evaluation during the extension periods.

To assess changes in symptoms and complications/comorbidities up to Week 16 on treatment with alpelisib as compared to placebo.

To assess changes in symptoms and complications/comorbidities associated with PROS over time.

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

Study design:

Phase II multi-center double-blind study with an upfront, 16-week randomized, placebo- controlled period and extension periods.

Study population:

Pediatric and adult patients with PROS.

Milestones:

Final clinical study report submission: 30-Sep-2030

CBYL719F12401 (EPIK-P3) summary

Study short name and title:
CBYL719F12401 (EPIK-P3): 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).

Rationale and study objectives:

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. Considering the debilitating nature of PROS, the aim of long-term treatment is to avoid worsening of the disease and is expected to improve symptoms, complications, co-morbidities and quality of life. Currently there are no clinical studies evaluating the effects of long-term treatment with alpelisib in PROS patients with severe or life-threatening conditions. Therefore, this study will provide information on the long-term clinical benefit and safety risks associated with alpelisib treatment.

Primary objective: To assess the long-term safety and tolerability of alpelisib over time in the prospective period.

Secondary objectives:

Retrospective period only:

To assess the safety and tolerability of alpelisib

Prospective period only:

To assess the safety and tolerability of alpelisib over time

Retrospective and prospective period:

To evaluate the long-term efficacy of alpelisib

To assess symptoms and complications/comorbidities associated with PROS over time

To assess the frequency of healthcare visits/hospitalizations due to PROS over time

- To assess type of medications and non-drug therapies over time

Study design:

The study is a Phase II multi-center, interventional (preceded by a retrospective non-interventional period), open label study, in pediatric and adult male and female participants with PROS. The study has an initial retrospective period and a subsequent prospective period.

EPIK-P3 will consist of the following: 1) an initial retrospective period and 2) a subsequent prospective period.

Retrospective period: The retrospective period of EPIK-P3 will collect key safety and efficacy data in participants previously enrolled in EPIK-P1 who received at least one dose of alpelisib under the temporary authorization for use or managed access program (i.e., in the context of routine medical practice by treating physicians) on or after 10-Mar-2020 (the day after the data cut-off date for EPIK-P1).

Prospective period: Starting from the enrolment date in the prospective period, safety and efficacy data will be prospectively collected following the structured plan outlined in the protocol.

Study population:

Paediatric and adult male and female participants with PROS aged ≥2 years who were previously enrolled in EPIK-P1 study and who continued to receive treatment with alpelisib after the 09- Mar-2020 cut-off date applied to EPIK-P1 study.

Milestones:

Final clinical study report submission: 30-Sep-2028

PRAC Rapporteur's conclusion

▪ Routine pharmacovigilance activities: The PRAC Rapporteur accepts the inclusion of an event specific follow-up checklist for the important potential risk 'Reproductive toxicity, including impaired fertility'. As this questionnaire contains specific questions that go beyond normal follow up of pregnancy cases (for example PROS disease history relevant to pregnancy or its outcome) **it is accepted that this routine pharmacovigilance activity is included in the RMP.**

▪ Additional pharmacovigilance activities:

The safety assessments within study EPIK-P1 were performed based on local medical practice and were collected retrospectively (by using medical chart data). Due to the retrospective nature of data collection in this managed access program, missing data were expected to be more common. At the moment it is unclear what the impact of missing data is on the determination of the safety profile and responses to the LoQ should be awaited before definitive conclusions can be drawn on the categorisations of the proposed PASS studies. The applicant provided the study protocol of the EPIK-P2 study. This phase II randomized, placebo controlled trial is included in the RMP as category 3 study. The proposed study design was discussed with ANSM in [2019], with AEMPS in [2019], and with EMA as part of CHMP scientific advice in [2020] and [2021]. The study design was also agreed with the FDA and is a post-approval requirement for the accelerated approval, which was granted on 05-Apr-2022. Within the study synopsis provided separately by the applicant, the applicant clarified that already two protocol amendments taken place in 2022 following FDA requests. At the moment of the last protocol amendment (28 Sep 2022) already 37 sites have been in initiated and 110 participants have been randomized/enrolled (47 in Group 1 [≥18 years]; 58 in Group 2 [6-17 years] and 5 in Group 4 [2-5 years).

The applicant plans to enrol approximately 189 participants in total, 78 adults and 111 children and adolescents. A total of approximately 156 male or female participants (of age ≥ 6 years) with PROS will be randomized in a 2:1 ratio in Groups 1 and 2 (approximately 78 participants per age group). Additional exploratory groups (Group 3, Group 4 and Group 5) will include approximately a total of 33 participants (approximately 12 in Group 3, 6 in Group 4 and 15 in Group 5). After Week 16 those participants who were randomized to receive placebo will be switched to active treatment with alpelisib in a blinded fashion at the dose level received at the end of the placebo period. Those participants who were randomized to receive alpelisib will continue their treatment at the same dose level. Follow up within this study can be up to 264 weeks (5 years). The estimated sample size and follow up seem sufficient to address the safety concerns in the RMP. Within the RfSI the applicant was requested to link the safety objectives of the study to the safety concerns in the RMP. Though the safety objectives were not linked to the safety concerns specifically, the safety outcomes outlined in the protocol will sufficiently cover the collection of data regarding the safety concerns. Furthermore, the applicant clarified that comprehensive analyses of safety data from the ongoing clinical studies (EPIK-P2 and EPIK-P3) will be performed to further characterize alpelisib identified and potential risks, including severe cutaneous adverse reactions, pneumonitis and any long-term effects on growth and development. The clarification of the applicant is accepted. However, comprehensive analyses of safety data from the ongoing studies (EPIK-P2 and EPIK-P3) should also be performed to further characterise the risk of Osteonecrosis of the jaw. Furthermore, the applicant was requested to specify how bone growth monitoring in paediatric patients will take place. This is assessed within question 64 and assessed by the CHMP rapporteur.

Information on safety in the PROS population derived from study EPIK-P1 is very limited. The MAH proposed two category 3 PASS studies in the RMP: EPIK-P2 and EPIK-P3 (estimated sample size 50 patient, follow up 5 years). Considering the randomised setting within EPIK-P2, the sample size and the follow up of 5 years it is anticipated that the EPIK-2 study will provide the most valuable information on

safety (including long term safety). The applicant stated in its response that the EPIK-P2 is intended to be the confirmatory study of the Conditional Marketing Authorization (CMA) application. As the primary objective and the key secondary objective of this study is efficacy related and the study is a condition to the marketing authorisation, this study should be included as a Post authorisation efficacy study (PAES) in the RMP. As this is a PAES assessment and approval of the study protocol will be performed by the CHMP Rapporteur (see

EPIK-P3:

Study CBYL719F12401 (EPIK-P3) will assess the long-term safety and efficacy of alpelisib 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. The applicant estimates that 50 patients will be included in EPIK-P3. Patients will be followed for at least 5 years. This study consists out of two parts: a retrospective and prospective part. Retrospective data will be collected from the compassionated use program up until enrolment in EPIK-P3. Upon enrolment in EPIK-P3, data will be collected prospectively. The primary objective of this study is to assess the long-term safety and tolerability of alpelisib over time in the prospective period.

The patients that already received alpelisib within EPIK-P1 cannot be included in the RCT EPIK-P2. It is therefore accepted that these patients are followed in a separate study. As newly treated patients will be recruited for the EPIK-P2 study, it is accepted that enrolment for the EPIK-P3 study is not open for new patients treated with alpelisib. As the EPIK-P2 study is expected to deliver the most valuable safety information due to the randomized nature, the larger sample size and the similar follow up of 5 years, it is accepted that the number of patients is limited in the EPIK-P3 study (50 patients). The inclusion criteria are acceptable. The exclusion criteria are extensive. However, these are generally in line with the exclusion criteria of EPIK-P1 study and the managed access program in which these patients have been included previous to the start of EPIK-P3. The applicant clarified that of the 57 patients who participated in EPIK-P1, 5 patients discontinued treatment prior to the cut-off date of EPIK-P1 (09-Mar-2020). Out of the remaining 52 patients, 48 patients (92.3%) were enrolled in EPIK-P3 across 6 sites in 4 countries. Four patients did not enrol into EPIKP3 for the following reasons: 3 patients did not give informed consent, and 1 patient was not able to participate as the study was declined by the respective site in Australia due to staffing issues. The in- and exclusion criteria are acceptable. However, the MAH is asked to confirm that all patients from EPIK-P1 that continued to be treated with alpelisib will be included in EPIK-P3. Furthermore, as the number of patients is already limited within EPIK-P3 the MAH is requested to clarify how many patients will be excluded for participation in this study (and for which reasons) based on the data available to the applicant at this moment.

Furthermore, it is accepted that this study is included as category 3 study considering that EPIK-P2 will provide the most valuable safety information and is a condition to the marketing authorisation. However, as this study will also provide information on pneumonitis, severe cutaneous adverse reactions and osteonecrosis of the jaw, the applicant should include severe cutaneous adverse reactions, pneumonitis and osteonecrosis of the jaw in the column safety concerns addressed in table 10-1 in the RMP. Furthermore, the MAH should submit interim analyses of this study within the PSURs. The milestones for these interim analyses should be included in the column due dates in table 10-1.

3.4.3. Risk Minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

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 Warnings and precautions
	PL Section 3 How to take Vijoice
	PL Section 4 Possible side effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk:
	• *SmPC Section 4.2 provides guidance on management of hyperglycaemia through alpelisib dose-modification and additional treatment*
	• *SmPC Section 4.4 provides guidance on precautionary measures, monitoring and handling of hyperglycaemia including the following:*
	  • *The awareness of possible severe hyperglycaemia events, including hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) or fatal cases of ketoacidosis observed in adult patients treated with alpelisib in the oncology setting.*
	  • *Recommendation to patients on lifestyle changes that may reduce hyperglycaemia (e.g. dietary restrictions and physical activity).*
	• *The need to optimize blood glucose before initiating treatment with alpelisib;*
	• *The need for regular, closer monitoring/ self-monitoring of fasting glucose levels frequently after initiation of alpelisib treatment, at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated, according to the instructions of a healthcare professional; and monitoring HbA1c every 3 months and as clinically indicated.*
	  • *The recommendation for diabetic or pre-diabetic patients, with a BMI ≥ 30 or age≥75 years (who may be more likely to develop severe reactions) to monitor /self-monitor fasting glucose daily for the first few weeks of treatment. Then continue to monitor fasting glucose as frequently as needed according to instructions by a healthcare professional with expertise on the monitoring and management of hyperglycaemia;*
	  • *Guidance on how to detect early signs and symptoms of hyperglycaemia and on fasting blood glucose monitoring is provided in PL section 2.*

	Other routine risk minimisation measures beyond the Product Information: None
Severe cutaneous 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 Warnings and precautions* Routine risk minimization activities recommending specific clinical measures to address the risk: *Guidance for the clinical management of severe cutaneous reactions is provided in the SmPC Section 4.4. including the following:* • *Alpelisib treatment should not be initiated and should not be reintroduced in those patients with a history of severe cutaneous reactions* • *The recommendation to advise patients of signs and symptoms of severe cutaneous reactions (e.g. a prodrome of fever, flulike symptoms, mucosal lesions or progressive skin rash): if those are present, alpelisib is to be interrupted and a consultation with a dermatologist is recommended* • *If a diagnosis of severe cutaneous reaction is confirmed, then alpelisib should be permanently discontinued* • *If severe cutaneous reaction is not confirmed, then alpelisib dose interruption, reduction, or discontinuation may be required.* Other routine risk minimization measures beyond the Product Information: *None*
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 Warnings and precautions Routine risk minimization activities recommending specific clinical measures to address the risk: • *Patients should be advised to promptly report any new or worsening respiratory symptoms.* • *In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, alpelisib treatment should be interrupted immediately and the patient should be evaluated for pneumonitis.* • *A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on*

	radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. • *Alpelisib should be permanently discontinued in all patients with confirmed pneumonitis.* Other routine risk minimization measures beyond the Product Information: *None*
Reproductive toxicity, including impaired fertility	Routine risk communication: *SmPC section 4.6 Fertility, pregnancy and lactation* *SmPC Section 5.3 Preclinical safety data* *PL Section 2 Warnings and precautions* Routine risk minimization activities recommending specific clinical measures to address the risk: • *Alpelisib is not be used during pregnancy and is not recommended in women of childbearing potential not using effective contraception.* • *The pregnancy status in females of reproductive potential should be verified prior to starting treatment with alpelisib.* • *Sexually-active females of reproductive potential should use effective contraception when taking alpelisib and for at least 4 days after stopping treatment with alpelisib.* • *Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking alpelisib and for at least 4 days after stopping treatment with alpelisib.* • *Females of reproductive potential should be advised that animal studies and the mechanism of action have shown that alpelisib can be harmful to the developing foetus. If alpelisib is used during pregnancy, the patient should be advised of the potential risk to the fetus.* • *Information provided in SmPC that based on repeat dose toxicity studies in animals, alpelisib may impair fertility in males and females of reproductive potential.* Other routine risk minimization measures beyond the Product Information: *None*
Safety with long-term use, including effects on growth and development	Routine risk communication: *None* Routine risk minimization activities recommending specific clinical measures to address the risk: *None* Other routine risk minimization measures beyond the Product Information: *None*

Additional risk minimization measures

Within the RMP of Piqray (alpelisib product approved within the breast cancer indication), educational material is included as an additional risk minimisation measure to mitigate the risk of serious (including life-threatening and fatal) hyperglycaemia events. The applicant did not propose additional risk minimisation measures to minimise the risks identified in the summary of safety concerns.

The applicant argued that educational materials are not warranted for Vijoice, as all necessary information to minimize and manage this risk is available to prescribers and patients in the current SmPC and Patient Leaflet (PL). Furthermore, the applicant argued that the frequency and severity of hyperglycaemia is lower in the PROS population compared to adult patients treated with alpelisib in the oncology setting because of the lower dosage and the lower prevalence of risk factors for hyperglycemia (i.e. diabetes, pre diabetes, BMI ≥30 or age ≥75 years) characterizing this population.

It is agreed that the reported frequency of hyperglycaemia with alpelisib is lower in the PROS indication (27% in adults) compared to the oncology indication (79%). However, it should be kept in mind that the exposure within the PROS population is still very limited. Exposure is especially limited in patients with diabetes type 1 or uncontrolled diabetes type II, as these are exclusion criteria for EPIK-P2. These patients will however not be excluded from treatment in the post-marketing setting, according to the proposed SmPC. Furthermore, no structured data collection has been performed within EPIK-P1 or in the compassionate use programs. At this moment, exposure is too limited to identify the more severe rare events related to hyperglycaemia which have been seen in the oncology population, such as ketoacidosis or Hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS). The argument that the patients in the PROS population have less risk factors for hyperglycemia as the majority are paediatric patients is acknowledged. However, according to demographic data from EPIK-P1 and EPIK-P2 studies, 31.6% were adult patient with a range from 18 to 50 years. Risks should be adequately minimised for the entire patient population.

Furthermore, the frequency of this risk could also be lower in the EPIK-P1 study as treating physicians are aware of the clinical recommendations to minimise this risk. This is not representative for the situation in clinical practice once this product is approved.

Furthermore, the proposed routine RMM for Vijoice are comparable to those for Piqray: information and clinical recommendations in the product information of Piqray with regard to hyperglycaemia is comparable with that proposed for Vijoice (Dose modifications, recommendation for monitoring of fasting glucose, life style changes, patients should be advised of signs and symptoms of hyperglycaemia, close monitoring of diabetes patients). The Applicant's approach to implement comparable routine RMM for both products but no comparable additional RMM is not considered acceptable. As hyperglycaemia is a known risk of alpelisib and serious cases (including fatal cases) of ketoacidosis have been reported in the oncology population and the data in the PROS population are too limited to exclude similar serious cases, it is considered that the risk of hyperglycaemia is not sufficiently minimised for Vijoice with routine risk minimisation measures only and a comparable health care professional brochure as implemented for Piqray should be included as aRMM to minimise the risk of hyperglycaemia for Vijoice. Key elements of this aRMM should be comparable with that of Piqray. Relevant other sections of the RMP should be updated accordingly.

No patient educational material has been implemented for Piqray because the risk minimisation measures described in the patient information leaflet were deemed sufficient at the moment of authorisation. As the risk minimisation measures to minimise the risk of hyperglycaemia with Vijoice are mainly focused on HCPs (Dose modifications, monitoring of fasting glucose, advising on life style changes, close monitoring of diabetes patients), it might be accepted that no educational materials for patients are warranted for Vijoice. However, the absence of educational materials for patients is only acceptable if the PIL provides comprehensive information to mitigate the risk of hyperglycaemia. In this regard, it is

noted that some discrepancies are noted between the SmPC and the PIL of Vijoice. Within the SmPC the term 'self-monitoring of fasting glucose according to the instructions of a healthcare professional' is used while no information is included regarding self-monitoring in the patient information leaflet. Furthermore, within the SmPC, the schedule of fasting glucose monitoring is presented but this schedule is not presented in the PIL. Information on the schedule of fasting glucose would be helpful for patients, if they are advised by their HCPs to self-monitor their fasting glucose. The MAH should therefore include information on self-monitoring of fasting glucose and the schedule of fasting glucose *monitoring in the PIL.*

3.4.4. Conclusion on the RMP

The PRAC Rapporteur, having considered the data submitted, is of the opinion that:

- the proposed post-authorisation PhV development plan might be sufficient to identify and characterise the risks of the product. However, satisfactory responses should be provided to the LoQ (**RMP OC**).

- the proposed risk minimisation measures are not sufficient to minimise the risks of the product and supplementary risk minimisation measures are required relating to the important identified risk hyperglycaemia (**RMP OC)**.

3.4.5. PRAC Outcome (March 2023)

At the March 2023 meeting, the PRAC fully endorsed the PRAC Rapporteur's assessment of the pharmacovigilance plan and risk minimisation measures of the RMP version 1.1 for Vijoice (alpelisib) submitted as part of this initial MAA (second round of assessment at Day 150) and supported the following approach:

Safety specification:

The PRAC acknowledged the assessment of the safety specifications by the CHMP Rapporteur and supported that osteonecrosis of the jaw is included as an important potential risk in the summary of safety concerns of the RMP. The Committee also noted the question raised by the CHMP Rapporteur, as a clinical safety concern, requesting the applicant to further discuss the potential risk of choking in the paediatric population especially for the younger patient population under 6 years of age, due to the currently developed film-coated tablets formulation.

Pharmacovigilance Plan:

The PRAC endorsed the proposed targeted follow-up questionnaires for the important potential risk of reproductive toxicity including impaired fertility as these will collect data beyond normal follow-up of pregnancy cases. Moreover, the Committee was of the view that the proposed EPIK-P2 study (*A Phase II double- blind study with an upfront, 16-week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics of alpelisib in paediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS)*) which would provide the most valuable information on safety including long-term safety and which might constitute the basis for a Specific Obligation in the context of the conditional MA, should be included in Part IV of the RMP as an imposed PAES since its primary and key secondary objectives are efficacy related. Furthermore, the Committee supported the inclusion of the EPIK-P3 study (*A phase II study to evaluate the long- term safety and efficacy of alpelisib in patients with PROS who previously participated in EPIK-P1 study*) as a category 3 PASS in Part III.

Risk Minimisation Measures:

The PRAC considered that routine RMM is not sufficient to mitigate the risks associated with the product. In line with the authorised alplesib product for the treatment of breast cancer (Piqray), the Committee supported that the applicant develops an HCP guide to minimise the important identified risk of hyperglycaemia with similar proposed key elements than the ones already agreed and implemented for Piqray and that these key elements for an HCP guide are to be included in PI Annex IID and RMP Annex 6. Moreover, the Committee was of the view that the absence of educational materials for patients regarding hyperglycaemia could be accepted pending that the Package Leaflet is amended to include adequate information on self-monitoring of fasting glucose and schedule of fasting glucose monitoring for patients, this would also bring consistency with the information included in the SmPC in this respect.

The RMP for Vijoice could only be considered acceptable once the RMP LoOI is fully addressed with the submission of a revised RMP version at the next round of assessment.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

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

4. Non-Conformity with agreed Paediatric Investigation Plan

Not applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

Vijoice (alpelisib) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor.

The target indication applied for by the applicant was modified to:

"Treatment of adult and paediatric patients aged 2 years and older with severe or life threatening PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy*".*

PROS is as a group of rare syndromes resulting from a genetic alteration in the PIK3CA gene The clinical characteristics of PROS can be diverse and depend on the timing of the mutation during embryogenesis and the organs affected. PIK3CA-related overgrowth spectrum is characterized by congenital or early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution. Segmental overgrowth is often congenital in onset, but is usually noted by 1 year of age with progressive overgrowth of tissues persisting in some cases into adulthood.

PROS syndromes are associated with cutaneous, vascular, musculoskeletal, and/or cerebral abnormalities, as well as focal or segmental overgrowth of the body. Complications of PROS depend on the anatomical site and extent of overgrowth, Functional impairment, renal impairment, cardiac

impairment, pain, recurrent superficial infections, impaired neurological development, seizures, thromboembolisms, pulmonary hypertension, and haemorrhages, amongst other manifestations can be a consequence of the overgrowth, all of which may be debilitating (particularly in the paediatric population), and may cause early mortality.

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. PIK3CA-related overgrowth spectrum may be conceived of 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 muscle can also be affected.

PROS includes diverse phenotypes, including (but not limited to): fibro-adipose hyperplasia or overgrowth (FAO), hemihyperplasia multiple lipomatosis (HHML), congenital lipomatosis with overgrowth, vascular malformations, epidermal nevi, and skeletal/scoliosis/spinal abnormalities (CLOVES) syndrome, macrodactyly, fibro-adipose 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), and lipomatosis of nerve (LON), and Klippel-Trenaunay syndrome (KTS).

5.1.2. Available therapies and unmet medical need

There is currently no cure for any of the disorders classified under the PROS umbrella nor any approved pharmacological treatment for the underlying disease in the EU. Current treatment comprises primarily of surgical debulking, along with orthopedic procedures to limit growth, and blocking of overgrowth vessels (sclerotherapy, endovascular occlusive procedure) which mainly addresses symptoms and complications of the disease. Regrowth following surgery occurs frequently and often requires repeated surgery indicating an unmet need for patients with PROS.

5.1.3. Main clinical studies

The main evidence of efficacy submitted is **EPIK-P1**. It is a retrospective chart review of patients 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 (n=7) 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. Fifty-two out of 57 subjects continue on treatment as of the DCO 9 March 2020. Of the 57 subjects included, 37 had at least one target lesion selected by imaging at the index date (by the 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 sign/symptoms, concomitant medication and functional status.

During the assessment period, the Applicant presented complete results of the retrospective period of an on-going Study with alpelisib (Study EPIK-P3), as supportive evidence. This is a Phase II multicenter, interventional, open-label study in paediatric and adult patients with PROS who participated in EPIK-P1, and who continued to receive treatment with alpelisib after the EPIK-P1 cut-off date (i.e., 09-Mar-2020). The study has an initial retrospective period and a subsequent prospective period. It is expected that approximately 50 patients may be enrolled in EPIK-P3. The purpose of this study is to assess the long-term safety and efficacy of alpelisib treatment. The patients will have data collected for approximately 2 years in the retrospective period and will be followed up for at least 5 years in the prospective period.

5.2. 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.

Supportive sensitivity analyses conducted based on the efficacy population (n=37), showed the extent to which the response rate is affected by the change in methods to deal with missing response (n=5). The resultant response rates range from 32.4% (worst case scenario) to 45.9% (best case scenario) and are consistent to the result of the primary analysis (37.5%).

The primary efficacy endpoint was reported for the following subgroups: age; sex; mutation type; PROS subtype; and lesion location. Consistent results were reported by sex. Given the low number of patients in some categories, no conclusions can be drawn for the subgroups based on age, mutation type, PROS subtype, and lesion location. Lower response rates were observed in the paediatric population, i.e. 30.4% (95%CI: 13.2, 52.9; 7/23 patients) in paediatric patients vs. 55.6% (95%CI: 21.2, 86.3; 5/9 patients) in adults.

Among the 12 patients with a response, the median DOR was not estimable as no events (progression or death) were 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, 23 patients (74.2%) had any reduction in the sum of target lesion volume and the mean (SD) percentage change, in the sum of target lesion volume (1 to 3 lesions), as assessed by ICRR was -13.66% (18.921).

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 (from 50% to 91%). The improvement was consistent across age groups in the full population.

Performance status at index time was available for 47 patients (82.5%), and at week 24 data were available for 24 patients. It was improved in 14 patients (21.3%) and stable in 10 patients (29.8%).

EPIK-P3 (retrospective period results):

Of the 57 patients who previously participated in EPIK-P1, 52 were eligible for participation in EPIK-P3 (at least one dose of alpelisib after the EPIK-P1 cut-off date (09-Mar-2020)), and 48 (34 paediatrics, 14 adults) consented to inclusion in the retrospective period of EPIK-P3. Median duration of exposure (from the start (10-Mar-2020) to the end of the retrospective period) to alpelisib in EPIK-P3 was 24.6

months overall (Min: 12 – Max: 28). Median duration of exposure since the start of alpelisib in EPIK-P1 up to the end of the retrospective period of EPIK-P3 was 43.5 months overall (Min: 29 – Max: 75).

The EPIK-P3 results show that most patients 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.

5.3. Uncertainties and limitations about favourable effects

No dose response studies were performed, the dose for paediatric patients (50 mg) corresponds to the lowest strength of alpelisib available at that time in clinical trials of alpelisib in breast cancer and the adult dose was the lowest dose used in these same studies.

The efficacy dataset is limited, as the pivotal efficacy data are derived from a single retrospective study with only 58 patients (treated, whilst primary efficacy outcome results are only available for 32 patients (complete case population)).

Of the 57 patients included in EPIK P1, 44 (77.2%) and 24 (75%) of the 32 patients included in the complete cases population were included in one site. This raises the possibility of bias related to the predominance of this centre especially in the context of a retrospective chart review study.

The open-label design of the study and the lack of external controls do not allow for population-level conclusions on the effect of alpelisib on tumour reduction. Further, in the absence of information on the natural history of these syndromes and considering the uncertainties regarding the proposed definition of response and the cut-off for its assessment whether the claimed responses can be isolated as a treatment-effect by alpelisib requires additional justification.

The pivotal study is a retrospective study and clinical outcomes were collected by physicians from the patient medical records and no questionnaire or scales were used to assess those clinical outcomes. Furthermore, the range of clinical outcomes is wide, and not specific to the PROS population. The absence of standardized data collection and the open label design of the study are prone for bias makes interpretation problematic and do not allow a clear conclusion on the clinical effect of alpelisib in the claimed population.

No pharmacokinetic studies in paediatric patients have been performed, the dosage was based on the lowest available strength of alpelisib available. Paediatric pharmacokinetic data will be collected in an ongoing phase 2 trial (EPIK P2) with first results expected in 2024.

All 12 patients who responded to treatment had CLOVES phenotype, no patients were considered responders in the other PROS phenotypes. This raises concern whether some benefit could be expected across the broad spectrum of PROS and patients regardless of the phenotype. Further, given the heterogeneity of presentation of PROS and the limited evidence provided, it would be relevant to fully characterise the subset of treated patients accounting for the "lesion related" outcomes to better understand and interpret treatment results. In this regard, no information on the tissue type involved in each lesion has been collected. This raises uncertainty as to whether some benefit could be expected across the broad spectrum of PROS and patients regardless of the tissue affected.

The primary efficacy endpoint was reported for the following subgroups: age; sex; mutation type; PROS subtype; and lesion location. Consistent results were reported by sex. Lower response rates were observed in the paediatric population, i.e. 30.4% (95%CI: 13.2, 52.9; 7/23 patients) in paediatric patients vs. 55.6% (95%CI: 21.2, 86.3; 5/9 patients) in adults. Within the paediatric population, the proportion of patients achieving a response varies 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

There are important uncertainties on whether the proposed posology in the paediatric population is an adequate one given the lack of PK data, the lower rates of responses observed in the paediatric population, doubts on the posology used in clinical practice (regardless of the recommended one) and lack of justification of the proposed dosing regimen in Section 4.2 of the SmPC.

The DoR was not reached and, taking into account the duration of the study and the number of patients included, the durability of the effect of alpelisib over time is not clear.

Supportive evidence provided is limited to the results from the retrospective period of EPIK-P3, which would support the benefit of alpelisib treatment and a favourable safety profile in the long term (total median duration of exposure 42 months, (Min:29 – Max: 75)). However, these results should be interpreted with caution given that these 48 patients represent the most favourable selected subset within the total treated population of 58 patients, 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.

5.4. Unfavourable effects

The safety profile of alpelisib in the currently proposed PROS indication is mainly based on retrospective data from 57 patients included in the EPIK-P1 study.

Out of the 57 patients, 82.5 % (n=47) experienced at least one adverse event and most of them were mild to moderate in severity. No discontinuation due to adverse events occurred but 10.5% patients (n=6) experienced at least one dose interruption for AEs. No action as regards alpelisib was undertaken in the majority of cases.

The most frequently AEs reported were under the SOC gastrointestinal (GI) disorders, general disorders and administration site conditions, infections and infestations, metabolism and nutrition disorders and skin and subcutaneous tissue disorders.

In paediatric patients, treatment-related AEs were reported in 23.1% patients (n=9) and the main reported events, were aphthous ulcer, stomatitis, and hyperglycaemia.

In adult patients, treatment-related AEs were reported in 72.2% patients (n=13), notably hyperglycaemia, aphthous ulcer, alopecia and cellulitis.

Overall, more than one-third of patients (36.8%, n=21) experienced a serious adverse event. Nevertheless, no treatment-related SAEs were observed in paediatric patients whilst in adult patients, treatment-related SAEs (all grades) included cellulitis, hyperglycaemia and venous thrombosis limb in one patient each.

Adverse events of special interest were characterized by a gastro-intestinal toxicity (nausea, vomiting and diarrhoea), hyperglycaemia, hypersensitivity, rash and stomatitis related adverse events. They are listed under the section 4.8 of the proposed SmPC.

Even though no AESI of pneumonitis and sever cutaneous adverse reactions were observed during EPIK-P1 study and as part of the compassionate use of alpelisib in PROS patients, they have been considered by the applicant as AESI in PROS patient with a statement in the SmPC and in the RMP as important identified risks.

As regards laboratory findings, blood calcium decreased, blood phosphorus decreased, blood creatinine increased, glycosylated haemoglobin increased and glucose increased were reported and listed under the section 4.8 of the proposed SmPC. Additionally, adverse events related to haematology disorders (e.g. decreased haemoglobin, decreased, lymphocytes and leukocytes decreased) occurred but no narratives have been found then, caul association with alpelisib could not be made.

The effects of alpelisib on growth and development are missing information in the safety concerns of the Risk Management Plan.

5.5. Uncertainties and limitations about unfavourable effects

Several limitations have been identified in this initial round, which need further discussion in order to obtain an adequate characterisation of alpelisib safety profile in the PROS indication. Some other concerns have been raised related to AEs that need further discussions from the applicant (e.g. dizziness, cellulitis, haemoglobin decreased).

Safety assessments in EPIK-P1 were performed based on local medical practice and were collected retrospectively (by using medical chart data). Due to the retrospective nature of data collection in this managed access program, missing data were expected to be more common. Therefore, imputation rules were pre-defined in the statistical analysis plan and applied for the safety evaluation. It is unclear what the impact of missing data is on the determination of the safety profile. This will remain a key uncertainty for the external validity of the safety data.

Furthermore, the long-term safety, notably its effects on growth and development in the paediatric population, remains an important uncertainty (presently data in cancer patient cannot allow any response to be given). No prospective, long-term, mature data are currently available, and they are not expected until 2028, at the earliest. This concern should be taken into consideration in the assessment of the benefit-risk balance of the requested indication**.**

5.6. Effects Table

Table 20. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Decrease tumour size	Proportion of patient with radiologic response	%	37.5% 95% CI: 21.2, 86.3	-	ICRR of imaging scans retrospective study Primary endpoint	Pivotal EPIK-P1 study
	DoR	weeks	Median not reached			Pivotal EPIK-P1 study
Unfavourable Effects : Adverse reactions >1%						
Blood phosphate decreased	Incidence of blood phosphate decreased	%	61	No control	These adverse reactions occurred after the introduction of alpelisib. Most of them have been reported in the breast cancer indication.	Pivotal EPIK-P1 study
Blood calcium decreased	Incidence of blood phosphate decreased	%	61	No control		
Increased glycosylated hemoglobin (HbA1C)	Incidence of Increased HbA1C	%	40	No control		
Blood creatinine increased	Incidence of Blood creatinine increased	%	35	No control		
Diarrhea	Incidence of	%	16	No control		
Stomatitis*	Incidence of stomatitis	%	16	No control		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hyperglycaemia	Incidence of hyperglycaemia	%	12	No control		
Blood glucose increased	Incidence of blood glucose increased	%	11	No control		
Headache	Incidence of headache	%	5	No control		
Dry skin	Incidence of dry skin	%	7	No control		
Alopecia	Incidence of alopecia	%	5	No control		
Nausea	Incidence of nausea	%	3.5	No control		
Vomiting	Incidence of vomiting	%	3.5	No control		
Dehydratation	Incidence of dehydratation	%	3.5	No control		
Decresed appetite	Incidence of decrease appetite	%	1.8	No control		
Acne	Incidence of acne	%	1.8	No control		
Rash Pruritus	Incidence of rash	%	Unknown		From compassionate use programs outside EPIK-P1. Twenty-four adverse events related to rash have been reported in 18 PROS patient.	CBYL719F12001M, CBYL719XFR01I and CBYL719X2001I

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

There is a rather solid 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 (commonly known as PROS). Alpelisib is an α-specific PI3K inhibitor, which has shown benefit in solid tumours (breast cancer), as well as in in vitro and in vivo nonclinical models of PROS.

The evidence provided to support the clinical efficacy of alpelisib in PROS in limited to a retrospective chart review of 57 subjects treated under the compassionate use programs across 7 sites in Europe. Forty-four of the total 57 patients (77.2%) were included in one site.

Of these 57 subjects, primary outcome results (radiologic responses) are available for a subset of 32 subjects. Of the 32 patients, 24 patients (75%) were included in one site.

The proportion of patients with radiologic 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 an independent central radiology review.

The single-arm study design can be understood based on the unmet medical need and the severity of the population included (PROS patients with severe or life-threatening complications). However, the lack of internal controls is not compensated for by external controls such as a natural history study, and this has an impact on the overall strength of the evidence.

The correlation between tumour decrease and clinical outcome is a major point for discussion. The observed difference between the general trend in unvalidated descriptive clinical endpoints and physician narratives showing improvement in patients, and the rate of responder based on ICRR is questionable. It is not clear whether such a correlation exists and whether the decrease in tumour size can be translated into improved clinical outcome in the claimed population.

The proportion of patients with response was lower in the paediatric patients compared to the adult group. Even if the numbers are low, the proportion of responders in the children group associated with the absence of PK data in paediatrics patients raise the question of the appropriateness of the chosen dose in the paediatric population and especially in younger patients.

No formal dose finding study was conducted, the dosage regimen used during the ATU program was mostly based on the lowest available strengths 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 (i.e. 250 mg).

All responders had CLOVES, no patients were considered responders in the other PROS phenotypes. It is unclear how the efficacy results, only observed in the CLOVES phenotype, can be generalized to the other subtypes There is no information regarding efficacy across different type of tissues because in EPIK-P1 the type of target lesions selected by the IRRC was not collected.

On a safety aspect, 82.5 % (n=47) experienced at least one adverse event. The most frequently AEs reported were under the SOC gastrointestinal (GI) disorders, general disorders and administration site conditions, infections and infestations, metabolism and nutrition disorders and skin and subcutaneous tissue disorders.

In paediatric patients treatment-related AEs were reported in 23.1% patients (n=9) and the main reported events, were aphthous ulcer, stomatitis, and hyperglycaemia.

In adult patients, treatment-related AEs were reported in 72.2% patients (n=13), notably hyperglycaemia, aphthous ulcer, alopecia and cellulitis.

Overall, more than one-third of patients (36.8%, n=21) experienced a serious adverse event.

Adverse events of special interest were characterized by a gastro-intestinal toxicity (nausea, vomiting and diarrhoea), hyperglycaemia, hypersensitivity, rash and stomatitis related adverse events.

As regards laboratory findings, blood calcium decreased, blood phosphorus decreased, blood creatinine increased, glycosylated haemoglobin increased and glucose increased were reported.

5.7.2. Balance of benefits and risks

There is a rather solid mechanistic rationale for the use of alpelisib in the treatment of PROS and data suggest that the tumour reduction observed in patients with PROS might be attributable to alpelisib based on the ICRR review.

However, the benefits/risk balance is currently uncertain as:

- the exact effect of alpelisib on the rate of progression of PROS is unclear considering that neither information on the rate of progression of PROS in patients prior to the initiation of treatment nor

regarding the natural history of these syndromes have been provided, that in the absence of a control group uncertainty remain that the claimed effect can be attributed to alpelisib;

- no clear correlation has been established between tumour decrease and the clinical outcome although a positive trend was reported in symptoms/signs;
- the extrapolation of the effects observed in CLOVES patients to the entire PROS population is questionable;
- there is lack of knowledge of results according to the type of tissue involved (e.g. vascular, adipose);
- the number of documented patients included in the application is low;
- there are uncertainties regarding the proposed dosage in the paediatric population;
- there are uncertainties as regards the long-term safety, notably its effects on growth and development in the paediatric population.

5.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

The applicant is requesting a CMA. The proposal to provide additional efficacy/safety data includes results from the following ongoing studies:

Study EPIK-P2: A prospective clinical Phase II study in patients 2 years and older with PROS (as agreed in the PIP). EPIK-P2 is a multicenter study with an upfront 16-week, randomized, double-blind, placebo-controlled period, and extension periods to assess the efficacy, safety, and PK of alpelisib in paediatric and adult participants with PROS (with symptomatic and/or progressive overgrowth and at least one measurable PROS-related lesion). In the confirmatory part of EPIK-P2, 156 participants, 78 adults and 78 children and adolescents, are planned to be enrolled. The study will have an overall follow-up of approximately 5 years to collect long-term safety and efficacy data. From a total of 156 patients planned to be enrolled, as of 03-Jan-2023, 150 patients have been enrolled, including 66 of 78 patients enrolled in Group 1, and Group 2 is fully enrolled with 84 patients.

The CSR for the primary analysis is expected to be available in ~Mar-2024 and the applicant intends to submit data from EPIK-P2 as a type II variation in Q2-2024. The final analysis CSR for EPIK-P2 is expected to be available in ~ Sep-2030.

Considering the randomised setting within EPIK-P2, the sample size and the follow up of 5 years it is anticipated that the EPIK-2 study will provide the most valuable information on safety (including long term safety). EPIK-P2 is intended to be the confirmatory study of the Conditional Marketing Authorization (CMA) application. As the primary objective and the key secondary objective of this study is efficacy related and the study is a condition to the marketing authorisation, this study should be included as a Post authorisation efficacy study (PAES) in the RMP. Of note, as this study will generate the most valuable safety information, PRAC Rapporteur will involve within the assessment of the safety part of this study with CHMP Rapporteur.

Study EPIK-P3: A Phase II multicenter, interventional, open-label study in paediatric and adult patients with PROS who participated in EPIK-P1, and who continued to receive treatment with alpelisib after the EPIK-P1 cut-off date (i.e., 09-Mar-2020). The study has an initial retrospective period and a subsequent prospective period. It is expected that approximately 50 patients may be enrolled in EPIK-P3; the final number of patients in EPIK-P3 will depend on the number of EPIK-P1 patients who continued to receive treatment with alpelisib after the cut-off date was applied for EPIK-P1 and who will provide their consent

for EPIK-P3. The purpose of this study is to assess the long-term safety and efficacy of alpelisib treatment. The patients will have data collected for approximately 2 years in the retrospective period and will be followed up for at least 5 years in the prospective period. Complete results of the retrospective period have been provided as part of the responses to the 1st LOQ. The prospective (interventional) period is ongoing, enrolment is complete (40 patients) and will assess the long-term (1st IA at 1 year, 2nd IA 3 years, final results 5 years) safety and tolerability of alpelisib over time. The CSRs are expected to be available in ~Sep-2024 (1st IA) and ~Sep-2026 (2nd IA), with final CSR expected to be available ~Sep-2028.

The product is not recommended for a conditional marketing authorisation as the benefit-risk balance is currently unknown (as discussed).

In light of the rarity of the disease, the retrospective nature of the pivotal study, study design, and the lack of comparator (internal or external), it is likely that uncertainties will remain; the need to consult an Ad Hoc Expert Group (AHEG) should be discussed by the CHMP. As a matter of fact, based on all the methodological uncertainties and limitations related to this application, an AHEG should be consulted given these ultra-rare conditions without any approved pharmacological treatment and with a high unmet medical need. A draft list of questions is proposed under section 1.1.

5.8. Conclusions

The overall benefit /risk balance of Vijoice proposed for the treatment of adult and paediatric patients aged 2 years and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) is currently unknown.