2 Synopsis

Name of product: Alpelisib

Protocol identification number: CBYL719C2404

Title of study: Alpelisib (Piqray®) Post-Authorization Safety Study (PASS): a non-interventional study of alpelisib in combination with fulvestrant in postmenopausal women, and men, with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), locally advanced or metastatic breast cancer with a phosphatidylinositol-3-kinase catalytic subunit alpha (PIK3CA) mutation, after disease progression following endocrine therapy as monotherapy, in the real-world setting.

Investigators:

Investigators who enrolled patients are listed below. Details of these investigators were specified in Appendix 16.1.4.

[redacted]
[redacted]
[redacted]

Study centers: The study was planned to recruit approximately 150 patients (i.e., 5 patients per month over 28 months to 30 months) across Europe. The following countries were considered for participation in the study: Austria, Netherlands, Norway, Sweden, Czech Republic, Denmark, Finland, Greece, Hungary, Italy, Poland, Croatia, Slovenia and Spain. A total of 4 patients were enrolled from 3 sites in Italy; however, only 2 of the 4 patients met the eligibility criteria.

Publication (reference): None.

Study period:

Study initiation date: 21-Jun-2023 (FPFV)

Early termination date: 18-Oct-2024 (LPLV)

Phase of development (phase of this clinical study): IV

Objectives:

The purpose of this clinical study report is to provide background of the study (including early study closure) and to describe the data from the CRF of the patients. Table 2-1 provides a list of the primary and secondary objectives and their corresponding endpoints.

Table 2-1 Study objectives and endpoints

Primary objective	Primary endpoint
To assess the incidence of hyperglycemia (AESI) observed during follow-up of patients	The incidence proportion of hyperglycemia (based on AE data).

treated with alpelisib in combination with fulvestrant.	
Secondary objectives	**Secondary endpoints**
To assess risk factors for hyperglycemia observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The risk factors of interest for hyperglycemia included: 1. Patient characteristics: age, calculated BMI, sex 2. Medical history: diabetes mellitus (including gestational diabetes), tobacco use, baseline diabetic status per laboratory values for HbA1c and FPG, clinically relevant self-monitoring test results (e.g., FG) 3. Family history of diabetes mellitus 4. Concomitant medications known to affect blood glucose levels: systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors
To estimate the incidence of complications of a non-compensated hyperglycemic state, such as ketoacidosis and HHNKS, observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion of ketoacidosis and HHNKS (based on AE data).
To assess the incidence of the AESI of ONJ, and the risk factors for ONJ observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion of ONJ (based on AE data). Risk factors for ONJ included: 1. Patient characteristics: age, calculated BMI, sex 2. Prior and/or concomitant use of bisphosphonates (e.g., zoledronic acid) 3. Prior and/or concomitant use of RANK-ligand inhibitors (e.g., denosumab)
To describe other AESIs of alpelisib in combination with fulvestrant observed during follow-up of treated patients.	The incidence proportion of AESIs: 1. GI toxicity (nausea, vomiting and diarrhea) 2. Rash 3. Hypersensitivity (e.g., anaphylactic reaction) 4. Pancreatitis 5. Pneumonitis 6. SCARs
To describe other safety and tolerability events observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion and severity of: 1. AEs 2. AEs leading to dose interruptions 3. AEs leading to dose reductions 4. AEs leading to permanent discontinuation of alpelisib in combination with fulvestrant 5. SAEs 6. Hematological and biochemical laboratory abnormalities

	To describe the duration of exposure to alpelisib in combination with fulvestrant.

Study design and methodology:

This study was designed as a prospective, multi-national, non-interventional study collecting data from postmenopausal women and adult men with HR+, HER2- locally advanced or metastatic breast cancer whose tumor harbors a PIK3CA mutation, who were to be treated with alpelisib in combination with fulvestrant after disease progression following endocrine therapy as monotherapy, in the real-world setting. The decision to treat the patient with alpelisib in combination with fulvestrant was made by the treating oncologist prior to and independent of the decision to enroll the patient into the study.

Physicians who used alpelisib in combination with fulvestrant in their routine clinical practice and were interested in participating in this study as investigators, were approached. Since the commercial availability of alpelisib was staggered based on approval and reimbursement timelines in individual countries, patients were recruited into this study after alpelisib was available in their individual country. Patients were allowed to participate in the study, if they fulfilled the eligibility criteria outlined below in the inclusion/exclusion criteria.

Patients were treated according to local clinical practice in the real-world setting. Hence, there were no examinations or laboratory tests performed specifically for this study. There were no mandated study visits. Data from all visits and communications (including telephone calls) with the treating oncologist from baseline through the end of study were collected.

It was planned that patients were to be followed from enrollment until 1) 30 days after alpelisib treatment discontinuation, or 2) death, or 3) lost to follow-up, or 4) patient withdrawal, or 5) physician decision to end treatment/study, or 6) end of the study, whichever occurred first. The end of the study was defined as a maximum of 12 months after the date the last patient was enrolled (LPFV); if the last patient was still on treatment on that date, they were not to be followed up any further.

Approximately 150 patients were planned to be enrolled into this study.

Diagnosis and main criteria for inclusion:

The inclusion criteria were:

1. Signed informed consent from the patient or a legally acceptable representative, obtained before any study-related activities were to be undertaken
2. Patients diagnosed with HR+, HER2- locally advanced or metastatic breast cancer with a PIK3CA mutation
3. Patients who had disease progression following endocrine therapy as monotherapy
4. Patients had to be postmenopausal women, or men, ≥18 years of age
5. Patients were to be recruited on or before their first prescribed dose of alpelisib in combination with fulvestrant

The exclusion criteria included:

1. Use of alpelisib prior to signing the ICF for this study
2. Participation in an interventional study within 30 days prior to the initiation of alpelisib

Treatment studied, dose and mode of administration: The study treatment was alpelisib (300 mg orally daily) in combination with fulvestrant (500 mg intramuscularly on Days 1 and 15 of the first 28-day cycle and then the first day of each cycle) as prescribed by the treating physician. Dose of each agent was based on the local prescribing information. Patients could continue all of their other concomitant medications as prescribed. No comparator cohort was included.

Protocol amendments and other changes to study conduct: This CSR describes the conduct of the study according to protocol v02 endorsed by the PRAC.

The original protocol dated 23-Mar-2021 was amended twice to address the PRAC comments as part of the EMEA/H/C/004804/MEA/002.1 procedure. The most recent Amendment was Amendment 2 dated 11-Nov-2021, that introduced update in the list of proposed countries and clarified that height and weight would be collected while BMI would be calculated. Previously in Amendment 1, dated 12-Oct-2021, main updates included the dates of study milestone dates, eligibility criteria (to fully match alpelisib EU SmPC), reduction in planned sample size (per feasibility assessment), clarifications on AE follow-up as well as cumulative incidence estimate regarding patients no longer enrolled, and confirmation that the type of HCP/physician who completes the CRF at respective sites would be reported in the study CSR (See Appendix 16.1.1 Protocol Table 3-1 for protocol amendment history details). On 05-Sep-2024, EMA agreed to remove the CBYL719C2404 study from the list of Piqray RMP PASS studies, as part of the EMEA/H/C/004804/II/0024 procedure. Study C2404 objectives on safety concerns related to the real-world usage of alpelisib would be assessed via routine pharmacovigilance activities. Subsequently, the study was closed early, on 18-Oct-2024. Due to the very low patient number (2 eligible patients), no statistical analyses could be performed.

A brief summary of the study is as follows:

As per the agreed Study C2404 protocol version 02, endorsed by EMA in Nov 2021, the proposed timeline for a FPFV was planned for May 2022 [Study C2404 protocol version 02].

The actual FPFV occurred on 21-Jun-2023. Out of the 277 sites identified, only 16 sites confirmed participation. Three additional patients were enrolled in Study C2404 for a total of 4 enrolled patients (out of an expected 150 patients). However, only 2 of the 4 patients were eligible.

The very low number of patients identified in the EU real-world setting may be explained by following reasons:

1. The change in the therapeutic landscape and in the clinical practice guidelines. The updated ESMO international consensus guidelines expert panel suggests that the most adequate sequence, in settings where availability of all drugs exists, is the use of a CDK4/6 inhibitor plus endocrine therapy as first-line, followed by alpelisib plus endocrine therapy in patients with PIK3CA-mutated tumors or everolimus plus endocrine therapy in patients with PIK3CA-wild type or unknown tumors (Cardoso et al, 2020) [1].
2. The restricted alpelisib indication approved in EEA countries (i.e., following endocrine therapy as monotherapy) (Piqray EU SmPC).
3. The reimbursement of Piqray for the indication approved in the EEA countries is limited and excludes major markets such as Germany and France.

Due to very low patient numbers (4 patients, including 2 eligible patients) no statistical analyses were performed. Database lock was achieved without all queries resolved. Data from the 4 enrolled patients are summarized below based on the data reported in the eCRF (filled eCRF included in Appendix 16.2.10).

Safety: Safety was monitored by assessing physical examination results, vital signs, performance status evaluations, laboratory evaluations for hematology and biochemistry (including glucose monitoring), and any AE reports from each visit. Data were collected on all AEs reported in the study. AESIs (hyperglycemia, ONJ, pneumonitis, SCARs, rash, hypersensitivity [e.g., anaphylactic reaction], pancreatitis, GI toxicity [nausea, vomiting and diarrhea]) were collected and graded using the CTCAE v4.03. Also, local laboratory data (especially toxicities) were summarized using the CTCAE v4.03, as per routine clinical practice, particularly for hyperglycemia.

Study investigators were responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance. Clinically significant abnormalities were recorded as either medical history/current medical conditions or AEs, as appropriate.

Statistical methods: The study planned to summarize the number and proportions of patients with hyperglycemia and other conditions mentioned in objectives (ketoacidosis, HHNKS and ONJ), and to describe the risk factors for hyperglycemia and ONJ as well as to fit logistic regressions for the above risk factors. Additionally, the study planned to describe the incidences of AEs and AESIs, and to summarize baseline characteristics of patients who developed AESIs (for more details refer Protocol Section 7.7 in Appendix 16.1.1).

However, since the patient number was very low, descriptive analysis could not be performed. Only 4 patients were enrolled and the planned interim analysis could not be pursued, therefore no SAP was developed.

Summary – Results

Efficacy results: Not applicable.

Pharmacokinetic results: Not applicable.

A summary of the data collected from the enrolled patients is provided below.

Patient [redacted]:

A [redacted]-year-old [redacted] patient was enrolled by an oncologist (primary specialty) in the study on [redacted]. [redacted] BMI was 23.51 kg/m^2 and ECOG performance status score was not available. The PIK3CA mutation was E545K. Prior endocrine therapies included letrozole [redacted] and an unspecified LHRH [redacted], ongoing at the end of study). The patient did not receive any prior CDK4/6 inhibitor treatment. Prior or concomitant medications (except those for AEs) included [redacted] and [redacted].

The patient started alpelisib at a dose of 300 mg daily on [redacted] and fulvestrant at a dose of 250 mg once every month on [redacted]; there was no change to the fulvestrant dose while the patient was on study.

On [redacted], the patient experienced multiple AEs including: cutaneous rash, hyperglycemia, and fever which led to alpelisib dose reduction to 150 mg daily from [redacted] to [redacted], followed by alpelisib dose interruption for 28 days (from [redacted] to [redacted]).

More specifically, the patient experienced Grade 3 cutaneous rash from [redacted] to [redacted]. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant. Treatment for this event included hydrocortisone, methylprednisolone, betamethasone valerate, cetirizine, and chlorpheniramine. The cutaneous rash improved to Grade 1 from [redacted] to [redacted], and was considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant.

With regard to other AEs, on [redacted], the patient experienced Grade 2 hyperglycemia which was reported as an "other medically important event," but was not recorded as a SAE per the CRF data. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant. The treatment for hyperglycemia included insulin, metformin, and semaglutide. After this event, from [redacted] to [redacted], the patient had blood glucose and HbA1c tests that were above the normal range, with the exception of one glucose test in [redacted]. The event hyperglycemia was considered not recovered/not resolved.

On [redacted], the patient also experienced fever lasting 1 day. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant. Paracetamol was administered on [redacted].

Treatment with alpelisib was restarted at a dose of 150 mg daily from [redacted] to [redacted], followed by increased dose to initial dosing level (300 mg daily) from [redacted] to [redacted].

Then, from [redacted] to [redacted], the patient experienced Grade 1 vomiting. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant. The patient received an unspecified antiemetic medication for vomiting.

On [redacted], the patient also experienced Grade 1 AEs of asthenia, nausea, and lack of appetite. All these events were considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant. The patient received unspecified support for the lack of appetite. These AEs led to alpelisib being temporarily

interrupted from [redacted] to [redacted]. The patient restarted alpelisib at a dose of 250 mg daily from [redacted] to [redacted]. The AEs of asthenia, nausea, and lack of appetite all resolved on [redacted].

The patient experienced an increase in the cutaneous rash to Grade 2, from [redacted] to [redacted]. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib and the relationship to fulvestrant was not assessable. Betamethasone valerate (Ecoval) was used for the event. From [redacted] to [redacted], the cutaneous rash became mild (Grade 1), considered by the Investigator as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant, and recovered.

From [redacted] till [redacted], treatment was temporarily interrupted for 35 days due to hyperglycemia and reinitiated at a dose of 200 mg daily from [redacted] till the end of study [redacted].

On [redacted], patient presented with Grade 1 AE of suspected (meaning unconfirmed) ONJ. It was considered, by the Investigator, as not suspected/not related to either alpelisib orfulvestrant, and no action with alpelisib or fulvestrant treatments were taken.

In summary, during the treatment with alpelisib and fulvestrant, the patient experienced multiple AEs, none of which were reported as SAEs, including cutaneous rash of various severity, hyperglycemia, asthenia, nausea, vomiting, lack of appetite, fever, and suspected (meaning unconfirmed) ONJ. Of these AEs, the events of cutaneous rash (Grade 3 – severe), hyperglycemia, nausea, and vomiting were considered as AESIs.

The patient had [redacted] last safety follow-up on [redacted], as the study was terminated by the Sponsor on this date.

Patient [redacted]:

A [redacted]-year-old [redacted] patient was enrolled by an oncologist (primary specialty) in the study on [redacted]. This patient's BMI was 28.08 kg/m^2 and ECOG performance status score was 1. The PIK3CA mutation was N345K. The patient's ongoing medical conditions included diabetes mellitus and hypertension. This patient's prior cancer-related surgeries included mastectomy in [redacted] and epidural and bone soft tissue excision on [redacted]. Prior antineoplastic therapies in the adjuvant setting included AC ([redacted] and letrozole ([redacted]). Prior antineoplastic therapies in the metastatic setting included exemestane ([redacted]), Faslodex ([redacted]), capecitabine ([redacted] to [redacted]), dorubicina liposomiale ([redacted]) and letrozole ([redacted] to [redacted]). This patient also received external beam as radiotherapy in [redacted] on [redacted], and from [redacted] to [redacted]. The patient did not receive any prior CDK4/6 inhibitor treatment. Prior or concomitant medications (except those for AEs) included [redacted]

The patient started alpelisib at a dose of 300 mg daily on [redacted] and fulvestrant at a dose of 250 mg once every month from the same date ([redacted]) with no changes to fulvestrant dosing during the study.

On [redacted], the patient experienced an AE of worsening of hyperglycemia (Grade 3). It was considered, by the Investigator, as suspected/related to the treatment with alpelisib as well as fulvestrant. Lantus was administered as treatment for the event.

On the same date, the patient experienced Grade 2 GI toxicity. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib and not suspected/not related to fulvestrant.

On [redacted], the patient presented with bilateral bronchopneumonia and was hospitalized (Grade 4 and a SAE). It was considered, by the Investigator, as suspected/related to the treatment with alpelisib as well as fulvestrant. Rocephin and oxygen were administered for the bilateral bronchopneumonia. On the same day, the patient also had Grade 4 respiratory failure which was considered, by the Investigator, as suspected/related to the treatment with alpelisib while not suspected/not related to fulvestrant.

Further, on [redacted], the patient had an event of Grade 4 acute renal failure. It was considered, by the Investigator, as suspected/related to the treatment with alpelisib while not suspected/not related to fulvestrant.

Alpelisib was interrupted on [redacted] due to all these events and never reinitiated by the end of study for the patient ([redacted]. All of these events recovered on [redacted] and all were considered as suspected/related to alpelisib. On [redacted], this patient had random glucose at 76 mg/dL (normal range: 74 to 106 mg/dL), which was not clinically significant.

In summary, during the treatment with alpelisib and fulvestrant, the patient experienced a total of 5 AEs, including 4 AESIs (worsening of hyperglycemia, GI toxicity, and bilateral bronchopneumonia and respiratory failure [both qualified as an AESI of pneumonitis]) and 1 non-AESI of acute renal failure. All these events were considered, by the Investigator, as suspected/related to the treatment with alpelisib. The events of worsening hyperglycemia and bilateral bronchopneumonia were also considered by the Investigator as suspected/related to the treatment with fulvestrant, whereas other events were considered as not suspected/not related to fulvestrant treatment.

The patient completed [redacted] last safety follow-up visit on [redacted].

Patient [redacted] (not eligible):

A [redacted]-year-old [redacted] patient was enrolled by an oncologist (primary specialty) in the study on [redacted]. This patient's prior cancer-related surgeries included right radical mastectomy in combination with ipsilateral axillary lymphadenectomy on [redacted]. This patient also received external beam as radiotherapy in [redacted] and from [redacted] to [redacted]. Prior antineoplastic therapies in the adjuvant setting included AC ([redacted] to [redacted]), TAXOTERE mono ([redacted] to [redacted]), and tamoxifene ([redacted] to [redacted]). Prior antineoplastic therapies in the metastatic setting included KISQALI ([redacted] to

[redacted]) and femara ([redacted] to [redacted]). Prior or concomitant medications (except those for AEs) included [redacted]

The patient started alpelisib at a dose of 300 mg daily on [redacted]. On the same day, fulvestrant was started at a dose of 500 mg once every 2 weeks in the first month and every month from following month; fulvestrant was ongoing at the end of study.

On [redacted] the patient experienced Grade 3 hyperglycemia which recovered on [redacted]. Treatment for hyperglycemia included varying doses of Toujeo SoloStar ([redacted] to [redacted], [redacted] to [redacted] and ongoing since [redacted]) and SLOWMET ([redacted] to [redacted]). Alpelisib treatment was interrupted for 24 days due to this AE and alpelisib was ongoing at the end of study. Hyperglycemia was considered, by the Investigator, as suspected/related to the treatment with alpelisib.

The hyperglycemia event was considered not suspected/not related to fulvestrant and no action was taken with fulvestrant due to hyperglycemia.

The patient had a protocol deviation as [redacted] did not meet the eligibility criteria related to prior antineoplastic medications and was discontinued from the study on [redacted].

Patient [redacted] (not eligible):

A-[redacted]-year-old [redacted] patient was enrolled by an oncologist (primary specialty) in the study on [redacted]. Prior antineoplastic therapies were all received in the metastatic setting, including femara and Kisqali ([redacted] to [redacted] for both), myocet ([redacted] to [redacted]), and exemestane ([redacted] to [redacted]). The patient also received external beam ([redacted]). Prior or concomitant medications included [redacted]

The patient started alpelisib at a dose of 300 mg daily on [redacted] and fulvestrant on the same date at a dose of 500 mg once every two weeks in the first month and every month from the following month; treatment with both the medications were ongoing at the end of study.

No AEs were reported.

The patient had a protocol deviation as [redacted] did not meet eligibility criteria related to prior antineoplastic medications and was discontinued from the study on [redacted].

Protocol deviations: A total of 3 protocol deviations were reported, of which 2 were critical and 1 was major.

Two critical deviations with respect to eligibility criteria resulted in 2 patients being discontinued from the study (patient IDs: [[redacted] and [redacted] as mentioned above). Both patients had previously been treated with a CDK4/6 inhibitor in the metastatic setting and, therefore, did not meet the study eligibility criteria. The study only included patients who had prior CDK4/6 inhibitor use as adjuvant treatment in the early breast cancer setting and then had progressed to locally advanced or metastatic breast cancer following endocrine therapy.

One major protocol deviation (Patient ID: [redacted] was reporting of SAE (bilateral bronchopneumonia) only through EDC within 24 hours but not through paper SAE form; this did not result in patient discontinuation from the study.

Conclusions: This early-closed study did not include statistical analyses due to the lack of adequate sample size. The safety events reported in the 4 patients in this study are aligned with the known safety profile of alpelisib; no new or unexpected AEs were reported.

Changes to the synopsis			
Version	Date (content final)	Summary of Changes	Change to overall conclusion
1.0	09-Apr-2025	Original version	NA

References:

1. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-49.