NOVARTIS

Clinical Development

Non-interventional study protocol (non-PASS) with secondary use of data

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

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List of abbreviations

AKT	Protein kinase B
BNP	B-type natriuretic peptide
CBC	Complete blood count
CCGs	CRF Completion Guidelines
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of federal regulations
CI	Confidence interval
CLOVES	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
CRF	Case report/record form
CRO	Contract research organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data management plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report/record form
EDC	Electronic data capture
ER	Emergency room
FAO	Fibroadipose overgrowth
FIL	Facial infiltrating lipomatosis
GPP	Guidelines for Good Pharmacoepidemiology Practices
HHML	Hemihyperplasia multiple lipomatosis syndrome
HRU	Healthcare resource use
ICMJE	International Committee of Medical Journal Editors
IC50	The half maximal inhibitory concentration
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional review board
KTS	Klippel-Trenaunay syndrome
LFT	Liver function tests
MAP	Novartis managed access program
MAR	Missing at random
MCAP	Megalencephaly capillary malformation syndrome
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
PASS	Post authorization safety study
PI3K	Phosphatidylinositol-3-kinase
PROS	PIK3CA-related overgrowth spectrum
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
U&E	Urea and Electrolytes

1 Responsible parties

N/A

2 Abstract

Title	Retrospective chart review study of patients with PIK3CA-Related Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program (EPIK-P1)
Version and date	Final: 04-May-2020
Name and affiliation of main author	PPD : PPD , Novartis
Rationale and background	See Section 4 for additional information. PROS describes a group of rare syndromes characterized by malformations and tissue overgrowth caused by somatic mutations in the PIK3CA gene. PROS is characterized by a high degree of inter-individual phenotypic heterogeneity attributed to the location and extent of overgrowth and degree of vascular complications. There is currently no approved pharmacological treatment for PROS; available treatment options are represented by de-bulking surgery, amputation, and/or endovascular occlusive procedures. Alpelisib has demonstrated antitumor activity in a variety of cancer cell lines, particularly those harboring PIK3CA mutations and in xenograft models with mutated or amplified PIK3CA. Venot et al. (2018) described the effectiveness of alpelisib in improving disease symptoms among nineteen patients with PROS receiving treatment under a compassionate use program. In these patients, previously intractable vascular malformations and overgrowths became smaller, congestive heart failure was improved, hemihypertrophy was reduced, and scoliosis was attenuated. The treatment was not associated with substantial side effects. This series of cases provides the first direct evidence supporting PIK3CA inhibition as a promising therapeutic option in patients with PROS. Novartis is sponsoring a managed access program (MAP) to allow treatment with alpelisib for patients with PROS. As of November 2019, 65 patients with PROS were expected to be treated with at least one dose of alpelisib at least 24 weeks prior to the planned cut-off date. Given the existing data in this very rare disease setting, Novartis will conduct a retrospective medical chart review to assess changes in clinical and functional outcomes as well as safety in patients with PROS treated with alpelisib.
Research objectives	See Section 5 for additional information. Primary objective 1. To describe the efficacy of alpelisib as measured by the proportion of patients with response (yes/no) at Week 24 (+/- 4 weeks), defined by achieving at least a 20% reduction from index date in the sum of measurable target lesion volume (1 to 3 lesions, via central review of imaging scans), provided that none of the individual target lesions have ≥ 20% increase in volume from index date and in absence of progression of non-target lesions and without new lesions (see Section 6.3 for additional information). Secondary objectives 1. To assess changes in the sum of measurable target lesion (1 to 3 lesions) volume over time 2. To assess changes in the sum of all measurable (target and non-target) lesion volume over time 3. To assess changes in the sum of all measurable non-target lesion volume over time

	4. To assess the duration of response defined as time from first documented response to the date of the first documented disease progression or death due to any cause. 5. To assess type of medication and non-drug therapies (e.g., concomitant PROS-related medications, PROS-related surgeries, duration of treatment/response) over time 6. To assess changes in PROS symptoms and complications (e.g., chronic bleeding/leaking, pain) over time 7. To assess changes in functional status (e.g., work/school/pre-school attendance, mobility) over time 8. To assess changes in Healthcare Resource Use (HRU; e.g., ER visits, hospitalizations) over time 9. To assess changes in clinical assessments such as laboratory evaluation, vital signs and physical findings over time 10. To assess the safety and tolerability of alpelisib
Study design	See Section 6.1 for additional information. This study will be a site-based retrospective non-interventional medical chart review of pediatric and adult male and female patients with PROS who initiated alpelisib at least 24 weeks before the cut-off date at a MAP site. The study cut-off date is 09-Mar-2020. Patient-level data will be abstracted from medical charts of all eligible patients at all participating sites. The pre-index (pre-baseline) period will be defined as the period from up to 24 weeks prior to the index date (baseline) through one day prior to the index date. The index date (baseline) is defined as the date of alpelisib initiation. The study period is the period from the index date up to the most recent data available at the time of the cut-off date (Figure 6-1). Information from patients treated with alpelisib will be used to describe the efficacy and safety of alpelisib in patients with PROS.
Setting and study population	See Section 6.2 for additional information. Patients will be included in this study if they meet all of the following inclusion criteria: • Patient (adult or pediatric) is ≥ 2 years of age* • Patient has a physician confirmed/documented diagnosis of PROS* • Patient has 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 on or before 23-Sep-2019 (ie: at least 24 weeks before the cut-off date of 09-Mar-2020) • Patient has medical chart history available during enrollment in the MAP • Patient (in case of pediatric patients assent and/or parent/guardian consent) consented to participate in the study (as required by local ethics regulations) *Inclusion criteria for MAP enrollment (assessed at the time of alpelisib initiation).

Study endpoints and variables	See Section 6.3 for additional information and list of variables Primary endpoint* 1. Proportion of patients with response (yes/no) at Week 24 (+/- 4 weeks), defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume (1 to 3 lesions, via central review of imaging scans), provided that none of the individual target lesions have ≥ 20% increase from index date and in absence of progression of non-target lesions and without new lesions (see Section 6.5 for additional information). *Target lesion volume may not be available for all patients (see Section 6.9 for additional information). Secondary endpoints 1. Percent change in the sum of measurable target lesion (1 to 3 lesions) volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date 2. Percent change in the sum of all measurable (target and non-target) lesion volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date 3. Percent change in the sum of all measurable non-target lesion volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date 4. Duration of response defined as the time from first documented response, to the date of the first documented disease progression or death due to any cause. 5. Change in type of medication and non-drug therapies (e.g., concomitant PROS-related medications, PROS-related surgeries, duration of treatment/response) over time 6. Change in PROS symptoms and complications 7. Change in functional status 8. Change in HRU 9. Change in clinical assessments such as laboratory evaluation, vital signs and physical findings over time 10. Type, frequency, seriousness, and severity per CTCAE v4.03 criteria and causality assessments of treatment-emergent adverse events
Data source	See Section 6.4 for additional information. The data for this study will be retrospectively abstracted from medical charts of eligible patients with PROS treated at participating clinical sites. Collected data will be converted to conform to CDISC data standards for electronic submissions.
Study size	See Section 6.6 for additional information. This study aims to collect medical chart information on eligible patients with PROS at participating sites, including all patients who have been treated with alpelisib. As a result, no formal sample size calculation has been performed. As of November 2019, 65 patients with PROS were expected to be treated with at least one dose of alpelisib at least 24 weeks prior to the planned cut-off date and will be potentially included in the trial.
Data analysis	See Section 6.8 for additional information. All analyses will be pre-specified in the statistical analysis plan (SAP). The primary and secondary analyses for this study will be descriptive in nature (estimation based), and therefore no hypothesis testing will be conducted. The data abstracted in this study will be summarized as appropriate. Descriptive analyses will be conducted where continuous data will be summarized by measures that may include the mean, SD, median, interquartile range (IQR), minimum, and maximum. Categorical and binary data will be presented by frequency counts and percentages. All descriptive analyses will be presented along with their 95% CIs as appropriate. The primary endpoint will be summarized and reported for the following subgroups: age, mutation type, lesion tissue type, and PROS subtype.

3 Amendments and updates

Amendment 01 (04-May-2020)

Amendment rationale

No patients have been enrolled and no patients are planned to be enrolled until after this amendment is approved and in place.

The changes implemented in this protocol amendment include the specification of a cut-off date (09-Mar-2020) in order to define the sample of patients to be enrolled in the study. This approach will allow Novartis to minimize the impact of the SARS-CoV-2 (COVID-19) pandemic on study integrity.

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 changes the cut-off date for the study to a fixed date of 09-Mar-2020. The assessment of response status is not expected to be impacted as all patients initiated alpelisib at least 24 weeks before 09-Mar-2020. This results in inclusion criteria number 5 being updated.

Following discussion with FDA, the primary analysis is modified. In the original protocol, the primary analysis was applying imputation of the missing volumetric assessments for target lesions at Week 24 (+/- 4 weeks), while in in the current version of the protocol a complete case analysis is utilized.

The complete case analysis is planned to be performed based on patients without missing response as defined in Section 6.8.1.

The analysis using imputed data will be performed as sensitivity analysis (instead of as primary analysis).

Duration of response is added to the secondary objectives as it is considered an important measure for the assessing benefit of the study drug.

Analysis of the secondary endpoints: for the endpoints related to objective #8, 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 will also be summarized and reported by sex.

To ensure consistent selection criteria, the target lesion selection will be performed by the independent central reviewer instead of the investigator.

Typographical and grammatical errors are corrected, and text has been reworded to add clarity where required.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of major change(s) that are made to the protocol:

- Abstract: Added new secondary objective (#4) for duration of response. Cut-off date changed from the abstraction date to 09-Mar-2020 for all patients. Index date noted as equivalent to baseline.
- Section 5.2: Added new secondary objective (#4) for duration of response.
- Section 6.1: Cut-off date updated from the date of abstraction to 09-Mar-2020 for all patients; rationale for the cut-off date change is provided. Definition of pre-index date period is further clarified. Index date noted as equivalent to baseline.
- Section 6.2.1: Inclusion Criteria 5 is updated; inclusion criteria 5 changes the abstraction date to the cut-off date (09-Mar-2020).
- Section 6.3: The cut-off date for the retrospective data collection has been updated from the start date of data abstraction to a universal cut-off date for all patients, 09-Mar-2020. The term "end of follow-up" is updated to "end of study". The Definition of "end of study" is clarified. Clarified that the eCRF will collect reasons for missing data for the Week 24 lesion assessment.
- Table 6-1: the word "end of follow up" has been changed as "end of study" and some wording has been added to clarify the time window around the last observation.
- Section 6.3.1: Patients who permanently discontinue alpelisib prior to 24 weeks of treatment and patients who required surgery as rescue therapy between index date and 24 weeks of treatment are defined as non-responders.
- Section 6.3.2: Secondary endpoint (#4) added for duration of response.
- Section 6.5: Name of imaging charter updated to "Independent Central Review Charter". Selection of target lesions changed from investigator responsibility to central reviewer responsibility.
- Section 6.7: Corrected the abstraction process to data entry instructions.
- Section 6.8.1: Target lesion selection was updated from the investigator selecting the target lesion(s) to the central reviewer selecting the target lesion(s). Redundant text is removed. Criteria defining non-responders were added. Definition of non-responders and missing response were added.
- Section 6.8.1.1: Sex added as criteria for a subgroup analysis.
- Section 6.8.2: Analysis of the secondary endpoints: for the endpoints related to objective #8, growth and development information were added to better characterize clinical assessments in patients who were aged <18 years at the time of alpelisib initiation. Duration of response was added as a secondary objective. Example intervals were updated. Severity clarified as toxicity grade. Text reworded for clarity. Examples updated to reflect eCRF design. Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest available MedDRA version at the time of the analyses will be used.
- Section 6.9: changed planned analysis from imputation method to complete case analysis
- Section 6.10.1: Data validation plan updated to data management plan or equivalent.

The changes to the protocol are considered to be substantial. This assessment is made to comply with the European legislation (Directive 2010/C 82/01/EC).

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do not affect the Informed Consent.

4 Rationale and background

PROS describes a group of rare syndromes characterized by malformations and tissue overgrowth caused by somatic mutations in the PIK3CA gene.

The umbrella term PROS encompasses a group of syndromes with diverse phenotypes, including (but not limited to) CLOVES, MCAP, HHML, FAO, hemimegalencephaly, FIL, KTS, and others.

In PROS, individuals' malformations are seen as overgrowth in several different tissues such as skin, vasculature, bone, fat, and brain tissue depending on the specific disease. Some of the malformations are congenital malformations of the vasculature causing excessive immature vasculature tissue, which may or may not be associated with overgrowth of other tissue. PROS is characterized by a high degree of inter-individual phenotypic heterogeneity attributed to the location and extent of overgrowth and degree of vascular complications. The rate and timing of excess growth is also variable, sometimes limited to childhood, while other patients have progressive soft tissue overgrowth during adult life. These rare conditions have no approved medical treatment and are associated with a number of complications which depend on the anatomical site and extent of overgrowth and vascular malformations. These complications may include functional impairment (e.g., impairment in walking or activities of daily living), pain, recurrent superficial infections, thromboembolism, bleeding and/or organ dysfunction, all of which may be debilitating, and cause early morbidity and even mortality (Parker et al. 2019). Current treatment includes surgical de-bulking procedures and amputation, and interventional procedures including sclerotherapy, laser and/or endovascular occlusive procedures. Regrowth following surgery occurs frequently and can require repeated surgery.

Sirolimus is an mTOR inhibitor that was introduced in 2011 as the first pharmacologic treatment for complicated vascular anomalies.

Sirolimus treatment has been shown to sequester components of mTORC2, which acts upstream on AKT signaling. However, it has not always been associated with lesion size reduction and has significant side effects, which include immunosuppression (Le Cras et. al. 2019).

Alpelisib is an oral α-specific class I PI3K inhibitor belonging to the 2-aminothiazole class of compounds. In biochemical assays, alpelisib potently inhibits the p110α subunit of PI3K (IC50 = 4.6 nM) ≥ 50-fold compared to the other class I PI3K isoforms (e.g., p110β IC50 = 1156 nM, p110δ IC50 = 290 nM, p110γ IC50 = 250 nM), and it is inactive against most other kinases (Fritsch et al. 2014). Alpelisib has demonstrated antitumor activity in a variety of cancer cell lines, particularly those harboring PIK3CA mutations and in xenograft models with mutated or amplified PIK3CA (Keegan et al. 2018). Clinical studies have also demonstrated the antitumor

activity of alpelisib, especially in tumors with PIK3CA alterations, with a favorable safety profile (Juric et al. 2019, Hoste et al. 2018).

Venot et al. (2018) described a postnatal mouse model of PROS/CLOVES that partially recapitulates the human disease. The model demonstrated the efficacy of alpelisib in preventing and improving organ dysfunction. The publication also describes how alpelisib was used in a compassionate use program to treat 19 patients (adult and pediatric) with PROS. This publication describes improvement in the disease symptoms in all patients receiving alpelisib treatment. Previously intractable vascular malformations became smaller, clinical complications such as congestive heart failure, hemihypertrophy and scoliosis improved. As reported in the publication, the treatment was not associated with substantial adverse effects. This series of cases provides the first direct evidence supporting PIK3CA inhibition as a promising therapeutic option in patients with PROS. It should also be noted that the 19 patients described in this publication are also intended to be included in this study through abstraction of data from medical charts into the study database.

Novartis is supporting compassionate use requests to allow for treatment with alpelisib for patients with severe and/or life-threatening PROS as part of an overarching MAP. As of November 2019, this program has approved requests for the treatment of over 100 patients from 14 countries, of which 65 patients were expected to be treated with at least one dose of alpelisib at least 24 weeks prior to the planned cut-off date. Considering the meaningful number of patients that are being treated globally with alpelisib under compassionate use programs in this rare indication, this retrospective chart review will describe clinical and functional outcomes as well as safety in patients with PROS before treatment with alpelisib and at key time-points after treatment initiation.

5 Research objectives

5.1 Primary objective

1. To describe the efficacy of alpelisib as measured by the proportion of patients with response (yes/no) at Week 24 (+/- 4 weeks), defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume (1 to 3 lesions, via central review of imaging scans), provided that none of the individual target lesions have ≥ 20% increase from index date and in absence of progression of non-target lesions and without new lesions (see Section 6.1 for additional information).

Target lesion volume may not be available for all patients (see Section 6.9 for additional information).

5.2 Secondary objectives

1. To assess changes in the sum of measurable target lesion (1 to 3 lesions) volume over time
2. To assess changes in the sum of all measurable (target and non-target) lesion volume over time
3. To assess changes in the sum of all measurable non-target lesion volume over time

4. To assess the duration of response defined as the time from first documented response (Section 6.8.2), to the date of the first documented disease progression or death due to any cause.
5. To assess type of medication and non-drug therapies (e.g., concomitant PROS-related medications, PROS-related surgeries, duration of treatment/response) over time
6. To assess changes in PROS symptoms and complications (e.g., chronic bleeding/leaking, pain) over time
7. To assess changes in functional status (e.g., work/school/pre-school attendance, mobility) over time
8. To assess changes in HRU (e.g., ER visits, hospitalizations) over time
9. To assess changes in clinical assessments such as laboratory evaluation, vital signs and physical findings over time
10. To assess the safety and tolerability of alpelisib

6 Research methods

6.1 Study design

This study will be a site-based retrospective non-interventional medical chart review of pediatric and adult male and female patients with PROS. This study will abstract longitudinal information that has been previously recorded in the medical charts of patients with PROS to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS.

Patient-level data will be abstracted from medical charts of all eligible patients at all participating sites and will be pooled and assessed. Trained personnel at each site will abstract medical chart data (see Section 6.4 for additional information). Informed consent will be obtained prior to data abstraction, as appropriate, for eligible patients interested in participating in the study.

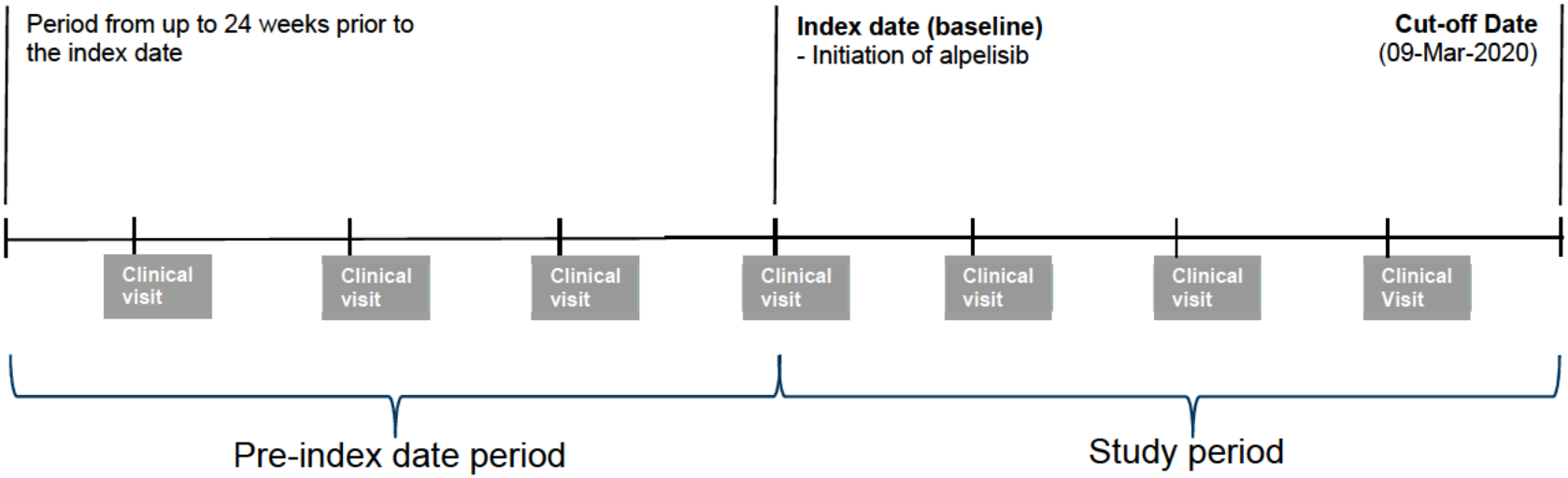
Patients with PROS who have received at least one dose of alpelisib initiated at least 24 weeks before the cut-off date will be included. The index (baseline) date will be defined as the date of alpelisib initiation. The pre-index date period will be defined as the period from up to 24 weeks prior to the index date through one day prior to the index date. The study period will be defined as the period from the index date up to the cut-off date (Figure 6-1).

The cut-off date (09-Mar-2020) is selected to minimize the impact of the COVID-19 pandemic on the data integrity. Eligible patients who initiated alpelisib on or before 23-Sep-2019 will have relevant assessments expected to occur on or before 09-Mar-2020. At that time of the cut-off, COVID-19 pandemic did not have major consequences on the regular management of the patients in the countries participating in the MAP.

Available information from all clinic visits during the pre-index date period will be abstracted; additionally, available prior PROS medications and PROS related surgical/vascular interventions will be collected since diagnosis.

During the study period, all available data will be collected from index date up to the cut-off date. If a patient has discontinued treatment prior to that date, only data reported up to 30 days after the last date of study treatment will be abstracted and entered into the database.

Figure 6-1 Study design



6.2 Setting and study population

Patients included will have received alpelisib through the following Novartis compassionate use program:

- **Managed Access Program (MAP):** The initial 19 patients described by Venot et al. (2018) received alpelisib under specific compassionate use regulations in France. Given the increase in compassionate use requests for the treatment of PROS following the publication by Venot et al. (2018), Novartis issued a global MAP extending the treatment available under this program to additional patients worldwide. It should be noted that the MAP is not a company-sponsored clinical study; rather, it provides common treatment guidance for physicians across the world requesting individual compassionate use under their local legislations with the physician ultimately remaining the "Sponsor".

6.2.1 Inclusion criteria

Patients will be included in this study if they meet all of the following inclusion criteria:

1. Patient (adult or pediatric) is ≥ 2 years of age *
2. Patient has a physician confirmed/documented diagnosis of PROS*
3. Patient has a documented evidence of a mutation in the PIK3CA gene*
4. Patient's condition was assessed by the treating physician as severe or life threatening and treatment was deemed necessary*
5. Patient has been treated with at least one dose of alpelisib, initiated on or before 23-Sep-2019 (i.e. at least 24 weeks before the cut-off date of the 09-Mar-2020)
6. Patient has medical chart history available during enrollment in the MAP
7. Patient (in case of pediatric patients assent and/or parent/guardian consent) consented to participate in the study (as required by local ethics regulations)
* Inclusion criteria for MAP enrollment (assessed at the time of alpelisib initiation).

6.2.2 Exclusion criteria

None

6.3 Study endpoints and variables

The study endpoints and variables listed below will be assessed during the pre-index date period and during the study period until the cut-off date. For reporting purposes, key time-points following the index date are defined and summarized in Table 6-1 along with their associated time windows. All time points available for each patient up to and including the cut-off date will be reported.

Table 6-1 Time windows for post-index date key-time point

Key time-points	Allowed windows
4 weeks	less than 10 weeks
12 weeks	10 or more, but less than 20 weeks
24 weeks	20 or more, but less than 28 weeks
36 weeks	28 or more, but less than 40 weeks

Key time-points	Allowed windows
52 weeks	40 or more, but less than 58 weeks
End of study	4 weeks prior to last observation - min (study treatment discontinuation + 30 days, cut-off date)

The last interval, referred to as "end of study" in Table 6-1, will include data available within the last 4 weeks prior to study treatment discontinuation plus 30 days or cut-off date, whichever comes first When a patient discontinues treatment data will be reported in the "end of study" time window as well as the one corresponding to the assessment (e.g., a patient discontinued treatment at week 58 data will be reported in the key point 52 weeks interval and in the "end of study").

The list of variables associated with each endpoint was developed based on a feasibility assessment conducted with the participating site with the largest number of patients treated with alpelisib (located in France) and four additional sites (located in Spain, Australia, Ireland, and the United States of America). Based on this feasibility assessment, the variables listed below are expected to be available for most patients across most sites. However, due to the heterogeneity of PROS manifestations, as well as variations in the patient follow-up schedule across MAP sites, information on certain variables may not be available or relevant to be collected for all patients included in this study. An expanded list of variables to be abstracted will be included in an annotated case report form.

All relevant and available information on the following endpoints and variables will be abstracted. When information is not recorded/available in the patient medical chart for the Week 24 lesion assessments, the reason for missing information will be documented. Missing data will be handled as described in Section 6.9.

In order to capture the heterogeneity of PROS and support a more complete description of the patient experience with PROS, demographic including race and ethnicity which were not described previously for this disease, and clinical characteristics as well as physician narratives, imaging scans, photographs, and/or videos taken in a clinical setting will also be abstracted, as available.

Patient characteristics will be described as of the index date, using the following information:

Demographic characteristics

- Month and year of birth
- Sex
- Ethnicity
- Race

Clinical characteristics

- Congenital/childhood onset
- Overgrowth sporadic/mosaic
- PROS sub-type (e.g. CLOVES, KTS)
- PROS diagnosis information (e.g. date of diagnosis, PIK3CA mutation(s), site of biopsy, diagnostic criteria utilized (Keppler-Noreuil et al., 2015))

- PROS disease characteristics (e.g. target and non-target lesions, number of lesions, location, lesion volume)
- Mosaicism proportion
- Comorbidities

Patient journey

- Physician narratives (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.
- Imaging scans, photographs and/or videos, where available with at least one corresponding baseline image/video.

6.3.1 Primary endpoint

The primary endpoint for this study was selected as it is an objective and quantitative outcome measure associated with manifestations of PROS that is observable in a significant proportion of the heterogeneous patient population eligible for inclusion. In addition, it is also associated with clinical benefit in patients with this condition (as documented in the Venot et al. (2018) publication).

1. Proportion of patients with response (yes/no) at Week 24 (+/- 4 weeks), defined by achieving at least 20% reduction from index date in the sum of measurable target lesion volume (1 to 3 lesions, via central review of imaging scans), provided that none of the individual target lesions have ≥ 20% increase from index date and in absence of progression of non-target lesions and without new lesions.

Patients who permanently discontinue alpelisib prior to 24 weeks of treatment, patients who required surgery as rescue therapy between index date and 24 weeks of treatment and patients with MRI scan performed at Week 24 for which the volumetric measurement cannot be calculated are defined as non-responders.

6.3.2 Secondary endpoints

The secondary endpoints for this study were selected to support the clinical risk/benefit of alpelisib and to supplement information obtained from the analysis of the primary endpoint. Secondary endpoints will be assessed during the study period and reported at pre-specified time-points, as described above in Section 6.3 (Table 6-1).

1. Percent change in the sum of measurable target lesion (1 to 3 lesions) volume, as assessed by a central review of imaging scans, as measured by the change between the index date (or up to 12 weeks prior) and key time-points following the index date
    - Target lesion volume as assessed by a central review of imaging scans on the index date (or up to 12 weeks prior) and at key time-points following the index date (Table 6-1)

2. Percent change in the sum of all measurable (target and non-target) lesion volume, as assessed by a central review of imaging scans, as measured by the change between the index date (or up to 12 weeks prior) and key time-points following the index date
    - All lesion volume as assessed by a central review of imaging scans on the index date (or up to 12 weeks prior) and at key time-points following the index date
3. Percent change in the sum of all measurable non-target lesion volume, as assessed by a central review of imaging scans, as measured by the change between the index date (or up to 12 weeks prior) and key time-points following the index date
    - Non target lesion volume as assessed by a central review of imaging scans on the index date (or up to 12 weeks prior) and at key time-points following the index date
4. Duration of response defined as the time from first documented response (Section 6.8.2), to the date of the first documented disease progression or death due to any cause.
5. Description of medications and non-drug therapy received at key points
    - PROS-related treatment(s) other than alpelisib
        - Medication(s) (e.g., concomitant PROS-related medications including medication for the management of PROS related complications as well as medications to manage complications secondary to alpelisib)
        - Non-drug treatment(s) (e.g., feeding tube, ketogenic diet, non-invasive device for sleep apnea, sclerotherapy, endovascular occlusive procedures)
    - Alpelisib treatment (e.g., dose, dose adjustments, duration of treatment, dose interruptions, discontinuation)
    - PROS-related surgeries (e.g., de-bulking or vascular surgery as well as the intended site of the procedure)
6. Change in PROS symptoms and complications over time
    - Overgrowth lesions, including number, girth, size, and color
    - Life-threatening complications (e.g., stroke, pulmonary embolism)
    - Chronic bleeding/leaking
    - Infection episodes
    - Hypotonia
    - Sleep disturbances
    - Seizures
    - Thrombotic events
    - Thromboembolic events
    - Pain
    - Cognitive impairment
    - Fatigue
    - Migraines
    - Depression/anxiety
7. Change in functional status
    - Work/school/pre-school attendance

- Mobility
- Performance status (e.g., ECOG, Lansky, Karnofsky score)

8. Change 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)
   - ER visits (including relevant medical interventions undertaken if related to PROS)
9. Change in clinical and laboratory assessments
   - Cardiac assessments (e.g., ECG, BNP)
   - Laboratory assessments (e.g., D-dimer, fibrinogen, hemoglobin, renal function, albumin, protein)
   - Vital signs (e.g., height, weight, blood pressure, resting pulse)
10. Type, frequency, seriousness, and severity per CTCAE v4.03 criteria and causality assessments of adverse events
    - Adverse events, including start and end date, grade, seriousness, relation to treatment, action taken with study treatment, and outcome

6.4 Data source

The data for this study will be retrospectively abstracted from medical charts of eligible patients with PROS at participating clinical sites and treated with alpelisib. The data will also include imaging scans (i.e., MRI, CT scans), clinical photographs and/or videos, as available. This data should be sent to the contracted vendor(s) as appropriate. Physician narratives will also be generated based on information recorded in the patients' medical charts and will be entered in the eCRF. A detailed training plan will be developed and all data abstraction will be conducted by trained personnel at each participating site using an electronic data capture system (EDC).

6.5 Central review of imaging scans

The volume of the target and all other measurable non-target lesion(s) will be assessed by a central imaging vendor and the details of this review will be captured in the Independent Central Review Charter. All available MRI scans, CT scans, and photographs will be shared with the vendor for assessment. Target lesions for the analysis of study endpoints will be independently selected by the central imaging reviewer using available images from up to 12 weeks prior to the index date, prior to any assessment of images from later in the study period. Central reviewers will take into consideration the clinical impact of the lesions.

6.6 Study size/power calculation

This study aims to collect medical chart information on patients eligible as per inclusion criteria with PROS at participating sites who have been treated with alpelisib. As a result, no formal sample size calculation has been performed. The precision of the estimate for different values of the response rate has been evaluated, assessing the widths of the 95% confidence interval (Table 6-2).

Based on the feasibility assessment conducted at each MAP site that has expressed interest in participating in this study in November 2019, the number of patients who satisfy the study inclusion criteria will be approximately 65. Assuming that between 15 to 20% of patients may not accept to participate in the study, 50 patients were considered for the estimation.

Table 6-2 Precision for binary outcomes using a 95% Confidence Interval (CI)

Sample size	Width	Response rate	Lower Limit	Upper Limit
50	0.237	0.200	0.100	0.337
50	0.267	0.300	0.179	0.446
50	0.284	0.400	0.264	0.548
50	0.289	0.500	0.355	0.645

6.7 Data management

The data management process will be pre-specified in data management plan (DMP) document(s) or equivalent.

DMP document(s) will describe key activities related to data management and will include a detailed description of the following steps/procedures:

- Systems used to collect, format, analyze, and report data (e.g., EDC Platform, SDTM conversion software, Analytic software)
- EDC (electronic data capture) implementation, users, and system access (e.g., the study team will ensure that training is provided to all EDC users as appropriate to each user's role; tracking of the name, role, and affiliation of all EDC users; following a database lock, the EDC database will be archived and stored on secure storage)
- Data review and cleaning process (e.g., each submitted eCRF will be reviewed and a list of queries resulting from the data review of each eCRF will be routed via the EDC platform to the site personnel). All necessary edits will be made in the EDC system by site personnel and will be automatically recorded with an audit trail, including the reason for change.
- Data entry instructions (CCGs)
- Database lock (e.g., following review and verification of the data, the eCRF of each patient on the EDC system will be locked after investigator signature has been obtained on the data entered)

6.8 Data analysis

All analyses will be performed by Novartis, and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

This section outlines the analyses that will be performed. The full analyses planned will be pre-specified in the statistical analysis plan (SAP). The SAP will be finalized and approved before the start of data collection.

The primary and secondary analyses for this study will be descriptive in nature (estimation based), and therefore, no hypothesis testing will be conducted. The data abstracted in this study will be summarized as described below. Descriptive analyses will be conducted where

continuous data will be summarized by measures that may include the mean, SD, median, IQR, minimum, and maximum. Categorical and binary data will be presented by frequency counts and percentages. All descriptive analyses will be presented along with their 95% CIs as appropriate.

Demographic and clinical characteristics, as described in Section 6.3, will be listed and summarized.

6.8.1 Analysis of the primary endpoint

The primary end point will be the proportion of patients with response at Week 24, as assessed by a central review of imaging scans. The primary analysis will be performed on all patients in the efficacy population without missing response (complete case analysis).

Definition of target lesion

In the medical record, it is anticipated that target lesions have been already selected by the treating physician based on the clinical/functional impact of such lesions on the patient. The clinical/functional impact will be 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.

However, the target lesions will be independently selected by the central imaging reviewer using pre-index date scans and clinical information regarding symptoms provided by the investigator. More details can be found in the Central Imaging Site Manual.

In addition to the above, the target lesion may 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 index date and ideally its size would be at least 2 cm in longest diameter at the index date (for each selected lesion)

Definition of non-target lesion

The non-target lesion consists of all other PROS-related anatomic lesions and may include the following:

- all anatomic lesions other than those selected as target lesions and may be measured at radiologic assessment (including lesions less than 2cm on MRI)
- anatomic lesions, limb/truncal areas affected by PROS, organomegaly when they may be measured only by caliper/ruler (e.g., circumference of changed limb or body part)
- truly non-measurable lesions (e.g., superficial visual lesions, masses, organomegaly, PROS-related enlargement of anatomic area identified by physical exam that is not measurable by reproducible imaging technique)

Analysis population(s)

The **full study population** will include all patients that satisfy the study inclusion criteria.

The **efficacy population** is a subset of the full study population, which will be used for the analysis of the primary endpoint and includes patients who meet the following criteria:

- Patient had at least one target lesion.
- Patient had an imaging scan performed on the index date (or up to 12 weeks prior to the index date) for at least one target lesion.

Definition of response

Patients included in the analysis population for the primary endpoint will be defined as responders if they meet all of the following criteria:

- Patient achieved ≥ 20% reduction from index date (or up to 12 weeks prior) in the sum of target lesion volumes (1 to 3 lesions, via central radiological assessment) by the change between the index date and 24 weeks (+/- 4 weeks) following the index date
- None of the individual target lesions has ≥ 20% increase from index date to Week 24 (+/- 4 weeks)
- Patient did not permanently discontinue alpelisib prior to 24 weeks of treatment
- Patient did not require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.
- No progression of non-target lesions at Week 24 (+/- 4 weeks)
- No appearance of new lesion at Week 24 (+/- 4 weeks)

Patients will be considered as having a missing response if volume assessment at 24 weeks (+/- 4 weeks) following the index date was not performed and:

- Patient did not permanently discontinue alpelisib prior to 24 weeks of treatment
- Patient did not require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.

Patients will be defined as non-responders in all other cases. In particular, patients with MRI scan performed at Week 24 (+/- 4 weeks) for which the volumetric measurement of the selected target lesions (1 to 3 lesions, via central radiological assessment) cannot be calculated will be considered as non-responders.

Disease progression at any assessment is defined as an increase of any individual target lesions of ≥ 20% in volume from previous assessment, progression of non-target PROS lesions or appearance of a new PROS lesion.

Relative to non-target lesions, progression will be assessed for the lesions that are identified at index date (or up to 12 weeks prior) with available information at Week 24 (+/- 4 weeks) and new lesions. At Week 24 the central imaging reviewer will make a conclusion if overall level of non-target disease burden decreased or increased unequivocally.

All patients in the efficacy population without a missing response will be used for the primary analysis of the primary endpoint (complete case analysis).

The overall efficacy will be described by considering the totality of evidence provided by both the primary and secondary endpoints, as well as physician narratives, clinical photographs and/or videos (if available) which will supplement quantitative findings and provide a more comprehensive assessment of the experience with alpelisib for patient with PROS.

Statistical methods

The primary endpoint will be assessed by a central review of imaging scans and summarized descriptively. No hypothesis testing will be performed. The response rate will be summarized using frequency counts and percentages along with 2-sided 95% CIs using the Clopper-Pearson exact method. Details on subgroups analyses and handling of missing values are provided in Section 6.8.1.1 and Section 6.9, respectively. Sensitivity analyses to assess robustness of the primary endpoint will be included in the SAP.

6.8.1.1 Subgroup analyses

The primary endpoint will be summarized and reported for the following subgroups:

- Age
- Sex
- Mutation type
- Lesion type (e.g., vascular, adipose)
- PROS subtype (e.g., CLOVES, KTS)

6.8.2 Analysis of the secondary endpoints

All the secondary endpoints will be reported using the full population.

Endpoint #1: Percent change in the sum of target lesion (1 to 3 lesions) volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date.

The endpoint will assess changes in the sum of target lesion (1 to 3 lesions) volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date (Table 6-1). The percent change in lesion volume will be assessed as a continuous measure over time. A graphical representation, such as box plots and spaghetti plot displaying the distribution in percent change at each time-point, will be provided to illustrate changes over time.

Endpoint #2: Percent change in sum of all measurable lesions (target and non-target) volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date.

The endpoint will assess changes in the sum of all measurable (target and non-target) lesion volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date (Table 6-1). The percent change in lesion volume will be assessed as a continuous measure over time. A graphical representation, such as box plots displaying the distribution in percent change at each time-point, will be provided to illustrate changes over time.

Endpoint #3: Percent change in sum of all measurable non-target lesions volume, as assessed by a central review of imaging scans, as measured by the change between the index date and key time-points following the index date.

The endpoint will assess changes in the sum of all measurable non-target lesion volume, as assessed by a central review of imaging scans, as measured by the change between the index

date and key time-points following the index date (Table 6-1). The percent change in lesion volume will be assessed as a continuous measure over time. A graphical representation, such as box plots displaying the distribution in percent change at each time-point, will be provided to illustrate changes over time.

Endpoints related to objective #4: Duration of response (DOR)

This analysis only applies to responders. The start date is the date of first documented response (Section 6.8.2), and the end date is defined as the date of the first documented disease progression or death due to any cause.

DOR will be listed and summarized for all patients in the efficacy set with response at any time. The distribution of duration of response will be estimated using the Kaplan-Meier method and the median will be presented along with 95% confidence interval.

Endpoints related to objective #5: Description in type of medication and non-drug therapies (e.g., concomitant PROS-related medications, PROS-related surgeries, duration of treatment/ response) over time

The endpoints for this objective will describe treatment patterns, including the use of PROS-related medications, including alpelisib and other non-drug treatments, such as surgeries.

The number (%) of patients who have at least one dose adjustment, interruption, or discontinuation, and their reasons, will be presented and summarized. In addition, the duration of treatment will be categorized into time intervals using appropriate units of time; frequency counts and percentages will be presented for the number (%) of patients in each interval.

The number (%) of patients who received any PROS-related medication other than alpelisib during the pre-index date period and the study period will be summarized in addition to the type of PROS-related surgery received and their reasons.

Endpoints related to objective #6: Change in PROS symptoms and complications

The endpoints for this objective will assess changes in PROS symptoms and complications (e.g., chronic bleeding/leaking, pain) between the index date and key time-points following the index date (Table 6-1). The number (%) of patients with each type of PROS symptoms and complications will be summarized as of the index date. Frequency counts and percentages will be presented by toxicity grade for each PROS symptom and complication.

Endpoints related to objective #7: Change in functional status

The endpoints for this objective will assess changes in functional status (i.e., work/school/pre-school attendance, mobility, and performance status) between the index date and key time-points following the index date (Table 6-1). The number (%) of patients attending work/school/pre-school will be summarized at the index date and at each time-point. In addition, the number (%) of patients with work/school/pre-school attendance (e.g., full-time; part-time, no attendance; part-time) will be presented at each time-point along with the reason for change status. Frequency counts and percentages will also be presented for the number (%) of patients with mobility between the index date and key time-points following the index date (Table 6-1). Performance status scores (i.e., ECOG, Lansky, Karnofsky) will be described and presented at the index date and at key time-points following the index date along with the number (%) of

patients with a change between the index date and key time-points following the index date (Table 6-1).

Endpoints related to objective #8: Change in HRU

The endpoints for this objective will assess changes in HRU (e.g., ER visits, hospitalizations) over time during the study period and key time-points following the index date (Table 6-1). The mean (SD) rate of hospitalizations and ER visits will be presented during the pre-index period and between the index date and over time during the study period. Frequency counts and percentages will also be presented for the number (%) of patients experiencing at least one hospitalization and at least one ER visit, separately, during the pre-index date period and study period. The mean (SD) number of ER visits and the mean (SD) duration of hospitalization will also be presented during the pre-index date period and over time during the study period.

Endpoints related to objective #9: Change in clinical assessments such as laboratory evaluation, vital signs and physical findings over time

The endpoints for this objective will assess changes in patient's clinical assessments (e.g., laboratory assessments, vital signs) between the index date and key time-points following the index date (Table 6-1). The change in clinical assessments will be summarized as the number (%) of patients experiencing a change in each clinical assessment. Changes in clinical assessments from the index date will also be presented as shift tables. Growth and development information will also be summarized for patients who were aged <18 years at the time of first dose and until the age of 18 years.

Endpoints related to objective #10: Type, frequency, seriousness, and severity per CTCAE v4.03 criteria and causality assessments of treatment-emergent adverse events

The endpoint will report adverse events defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur during the study period. As much as possible, each adverse event will be evaluated to determine:

1. Toxicity grade
2. Duration
3. Relationship to the study treatment (i.e., not related, related, unknown)
4. Whether it is serious as per medical chart (seriousness and seriousness criteria established during the MAP)
5. Action taken with respect to study treatment (i.e. dose increased; dose not changed; dose reduced; drug interrupted; drug withdrawn)
6. If a concomitant medication or additional therapy was provided (for example diet for impaired glycemic control)
7. Outcome (i.e., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

Adverse events will be summarized as: the number (%) of patients experiencing each adverse event, (the number (%) of patients experiencing any CTCAE grade 3 or higher adverse event, the number (%) of patients with serious adverse events, the number (%) of events related to treatment, the number (%) of patients who received a concomitant or an additional treatment

due to adverse event. For adverse events requiring dose interruption, the duration of interruption will be reported.

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest available MedDRA version at the time of the analyses will be used.

The outcome of adverse events will be presented as the number (%) of patients with each outcome after any event (e.g., number [%] of patients that did not recover from any event).

Undesirable medical signs identified by investigational results (such as vital signs, blood and urine laboratory, ECG, imaging) will be captured with the most appropriate adverse event term.

6.9 Handling of missing data

As this is a retrospective non-interventional study, information may not be systematically collected, resulting in some missing data. Methods of handling missing data for each of the study variables will be detailed in the SAP.

Imaging scans for all measurable lesions may not be available for all patients on the index date. In such cases, the most recent imaging scan conducted during the 12 weeks prior to the index date will be considered as the imaging scan performed on the index date for these patients. This 12 -week window is being utilized based on feasibility assessment of the likelihood of imaging being available at index date and a reasonable time period in which to review imaging data in the pre-index period.

All data available for each patient and each variable will be collected during the pre-index and the study period; appropriate key time-points and associated time windows for the study period (Table 6-1) will be used to analyze the secondary endpoints given there is no common assessment schedule in clinical practice. The number of patients with missing values will be reported.

For the primary analysis, all patients in the efficacy population without missing response will be used (complete case analysis).

Supportive analyses will be performed to investigate the robustness of the primary analysis using the full efficacy population. In particular, a sensitivity analysis will be performed where missing volumetric assessments at Week 24 will be multiply imputed based on a missing at random (MAR) assumption for patients with missing response. The imputation model will include the longitudinal volumetric measurements (i.e. the MRI scans at index date and at Week 48), the measurement at index date, as well as covariates such as age. Additional details will be provided in the SAP.

No imputation will be performed for the non-target lesions, only lesions that have data at index date (or up to 12 weeks prior) and at weeks 24 (+/- 4 weeks) will be used to define progression.

6.10 Quality control

Quality control measures will be implemented throughout all steps of the development and implementation of the eCRF as well as data collection, cleaning, and analysis.

While developing the eCRF, data validation checks at the point of data entry will be implemented to prevent “out of range,” “missing,” or other checkable data entry errors (e.g.,

ensuring that the age of patients meets eligibility criteria and that the dates entered for key events are chronologically accurate) to determine if entered data have internal conflicts. These consistency checks will be used as soft warnings (e.g., messages notifying a potential issue with the chronology of events and to revise the answer) while data abstractors complete the eCRF.

The eCRF will be developed using an EDC platform, which is compliant with Title 21 of the Code of Federal Regulations (21 CFR Part 11). The EDC platform is a validated data capture software, which features electronic data capture, data change tracking, electronic signatures, and audit trail capabilities. The software allows for the creation of data checks and other features to support data quality, such as automated consistency checks (e.g., consistency and range checks) and "unknown/missing" options for data input. The platform will also allow for post-hoc manual review of data for outliers and other inconsistencies not flagged in real-time and will prompt remote follow-up with investigational staff to review the outliers and inconsistencies and confirm/revise their previous entries in the EDC platform. For tracking purposes, a query log and an audit log will be retained to maintain a log of all queries and changes in data during the quality control process.

Upon receipt of the data, the study team will make a copy of the raw data and store it in a restricted access folder and confirm that all expected data and variables are included, checking for completeness of all variables. Identified outliers and other data inconsistencies not flagged electronically will be manually cross-checked with records for all subjects in coordination with the sites to resolve identified data issues. Any necessary modifications will be recorded in the EDC by the site and in the EDC audit log along with the reason for change.

6.10.1 Data quality management

Novartis Data Management or designated CRO will assure database quality processes are followed including review of the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data management plan or equivalent.

6.10.2 Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file.

The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. No information in source documents about the identity of the patients will be disclosed.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents. Essential documents (written and electronic) should be retained for a period of not less than twenty five (25) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

6.10.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

Novartis Trial Monitoring / designated CRO will assure compliance monitoring.

6.11 Data reliability and relevance to address the research objectives

The variability amongst PROS patients in symptomatology and personalized treatment may result in difficulty identifying an average treatment effect.

Measures to address additional concerns regarding various types of biases (e.g. selection, investigator bias) arising from retrospective studies are detailed. All patients satisfying the inclusion criteria as outlined in Section 6.2 are included in the chart review study. However, note that all patients from the MAP who started alpelisib treatment at least 24 weeks ago will be contacted to be part of the chart review study i.e., no pre-selection of MAP patients will be made. In addition, the investigator bias for the primary outcome measure is mitigated by instituting an independent panel of radiologists who will review the target and non-target lesions based on available imaging scans. Furthermore, data reliability, completeness and consistency checks are detailed in Section 6.10 and will be further explained in the DMP.

7 Protection of human subjects

This study was designed and shall be implemented and reported in accordance with the GPP of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE guidelines (Von Elm et al. 2007), and with the ethical principles laid down in the Declaration of Helsinki.

Due to the limited number of patients with PROS currently receiving alpelisib treatment through a Novartis MAP, data abstracted as part of this study may be deemed personally identifiable at some or all clinical sites.

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB) / Institutional Ethics Committee (IEC) approved informed consent (assent for pediatric patients) unless this is not required per local laws and regulations.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

The date when a subject’s Informed Consent / Assent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators in a separate document a proposed informed consent / assent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study.

Patients may obtain a copy of their information that has been entered as part of this study at any time. Patients may also decide to rectify, oppose, delete, or limit this information at any time and at no consequence to themselves.

Participating clinical sites will be responsible for identifying requirements at their institution (e.g., IRB/IEC application), collecting informed consent specific to the current study (as necessary), and submitting required documents to the relevant authorities (as necessary).

8 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, no individual safety reports will be made. Safety events and other safety-relevant results will be provided down to an individual level in datasets in the study report. Adverse events are collected from the index date through 30 days after the last dose of study treatment until the cut-off date. If any death occurs after the cut-off date but within 30 days after the last dose of alpelisib, this event should still be reported.

In studies based on secondary use of data with a safety-relevant result, reports of adverse events/adverse reactions will be summarized in the study report (i.e., only the overall association between an exposure and an outcome will be presented). Relevant findings from the study report can be included in the periodic aggregated regulatory reports submitted to Health Authorities by Novartis.

9 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines. In addition, results obtained from the current study are intended for submission as primary data to health authorities worldwide.

No individual investigator may publish on the results of this study without prior approval from Novartis.

10 References

Available upon request

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