NOVARTIS

Clinical Development

Alpelisib (BYL719)

CBYL719F12002 / NCT04285723

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)

Statistical Analysis Plan

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Version history

Date	Reason for update	Introduced changes	Section and title impacted (Current)
18-Feb-2020	First version	Not applicable	Not applicable
26-May-2020	Amendment 1	• Replace abstraction date with cutoff date to reflect protocol amendment • Amendment of study date definitions • Inclusion of non-response and missing response definition • Primary analysis based on complete case analysis • Multiple imputation analysis is now a sensitivity analysis • Duration of response added as secondary endpoint • Events for duration of response modified as to includes death due to any cause • Derivation of dose intensity(DI) and relative DI (RDI) is added • Inclusion of vital signs for pediatric patients is added • Wording around growth data is added • List of AESI is amended • Analyses of time to first AESIs are added [redacted] • Appendix is added to incorporate general definitions and conventions • Details on growth chart are added	1.3 Study design and settings 3.5 Primary endpoint 3.5.1 Handling of missing data for primary endpoint 3.5.2 Sensitivity and supportive/supplemental analyses 3.6 Secondary endpoints 5. Appendix

07-Aug-2020	Amendment 2	• Added a protocol deviation section	3.4 Patient disposition, demographics and other baseline characteristics
		• [redacted]	[redacted]
		• Deleted text "AE leading to fatal outcome" from AE summaries that will be produced. This information will only be listed. • Number of occurrences for SAE sentence deleted. This summary will be produced separately and not as part of the CSR. • Added information and reference for the standard deviation score (SD- score)	3.6Secondary endpoints
		• Clarifications and corrections around time windows and dates imputations rules	3.3 Key post index date time points for reporting endpoint over time 3.5.4Subgroup analyses for the primary endpoint Appendix 4.3
19-Mar-2021	Amendment 3	• Added a description of the changes to the protocol specified analysis related to the baseline and 'week 24' time windows and	2 Changes to the protocol specified analysis

	provided the rationale for the revision.	
	• Replaced Week 24 (+/- 4 weeks) with Week 24 or 6 months (+/- 4 weeks) throughout the text as appropriate.	1.2 Study objectives; 3.5Primary endpoint 3.5.1Definition of response 3.5.2Handling of missing data for the primary endpoint 3.5.3Sensitivity and supportive/supplemental analyses
	• Extend the time window for the baseline imaging scans to include imaging scans performed up to 24 weeks prior to index date window.	3.2Analysis population(s)
	• Added: "Only the time points with at least 10% patients will be displayed in the corresponding output." • Updated Table 3-1 with new time windows Week 24	3.3 Key post index date time points for reporting endpoint over time
	• Extend the time window for the '24 weeks' scan to include imaging scan assessments between 20 weeks and 31 weeks for the primary endpoint as well as other endpoints.	3.5Primary endpoint
	• Updated the definitions for 'responders', 'non-responders' 'missing response', and 'progression' of non-target lesions based on the revised time window for 'week 24' • [redacted]	3.5.1 Definition of response

	[redacted] • Deleted "categorical data" from the following sentence: "The Clopper-Pearson exact method will be used to estimate 95% CIs for binary data". There are no categorical data in the primary end point.	
	• In Table 3-4 added the proportion of patients with “High”, “Medium” and “Low” impact to report of symptoms and complications. • In Table 3-4 modified the proportion of patients with a change in pain severity score from index date with the proportion of patients with improvement, worsening and no change in pain severity. • In Table 3-4 added the pain reduction. • Added text to clarify the reporting of the pain questionnaires and specified that pain severity will be reported at 12, 24, 52 weeks windows and the “End of study” and all other time points will be listed. • Added text to report pain reduction and to describe how pain reduction is calculated. • Modified text related to secondary objective #7 and text in Table 3-5 by reporting the proportion of patients with improvement,	3.6 Secondary endpoints

		worsening and no change in functional assessment (ECOG, Karnofsky, Lansky) instead of the mean change in score from index date. • Added definition for improvement, worsening and no change in functional assessment for each scale (ECOG, Karnofsky, Lansky) • Modified the text related to secondary objective #7 and the text in Table 3-5 by reporting the percentage of patients reporting improvement, worsening or no change in work/school attendance instead of the percentage of patient that attend work/school/pre-school. • Clarified that the reason for change of work/school attendance will no longer be presented in a tabular format but listed instead. • Specified that the improvement, worsening or no change for performance status and work/school attendance will be reported at index date, baseline, 12, 24, 52 weeks windows and the “End of study”. • Added definition of impact to complement the reporting of secondary objective #10 • Data analysis of AESIs: deleted the	3.6 Secondary endpoints

time to first occurrence of CTC grade 2 for AESI; • Data analysis of AESIs: deleted the duration of first event for CTC grade 2 or worse diarrhea (preferred term) and grade 2 or worse rash (preferred term). • Corrected " by treatment group" with "by age group"	
[redacted]	[redacted]
• Updated list of variables with partially missing start and/or end dates that are imputed in Table 4-1 and Table 4-2 respectively. • Added Table 4-3 to address imputation of partially missing start dates for variables for which an end date is not planned to be collected (e.g. death).	Section 4.3 Imputation rules
• Added a section to describe how partially missing dates are associated to pre-index or study period.	Added Section 4.3.1.1 Imputations and study periods (pre-index, on study)
• Added link to WHO website for growth chart.	Section 4.5
• Added references for the ECOG and Karnofsky scale correspondence, and for the Important Medical Event list.	Section 5 Reference

07-Jul-2021	Addendum 1	• For the ECOG scale the following has been corrected: in the previous SAP version (Amendment 3) “improvement” was defined as an increase and “worsening” as a decrease, in the current version “improvement” is correctly defined as a decrease and “worsening” as an increase. • For the Wong Baker, the FLACC and the Numerical pain scales the following has been corrected: in the previous SAP version (Amendment 3) “improvement” was defined as an increase and “worsening” as a decrease, in the current version “improvement” is correctly defined as a decrease and “worsening” as an increase. • The category referred to as “no change” for work/school, pain severity and performance status questionnaires was renamed as “stable” for consistency throughout the document. Derivation remains the same. • Reporting of the duration of exposure has been updated to be in “months” instead of “weeks”.	Section 3.6 Secondary endpoints

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BMI	Body mass index
BNP	Brain natriuretic peptide
CI	Confidence interval
CLOVES	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
CRF	Case report/record form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report/record form
EDC	Electronic data capture
ER	Emergency room
FAO	Fibroadipose overgrowth
FDA	United States Food and Drug Administration
FIL	Facial infiltrating lipomatosis
HHML	Hemihyperplasia multiple lipomatosis syndrome
HRU	Healthcare resource use
IC50	Half maximal inhibitory concentration
ID	Identification
KTS	Klippel-Trenaunay syndrome
MAP	Managed access program
MCAP	Megalencephaly capillary malformation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
N/A	Not applicable
NGS	Next-generation sequencing
PDS	Programming Datasets Specifications
PI3K	Phosphoinositide 3-kinases
PIK3CA	Phosphatidylinositol-3-kinase catalytic subunit alpha
PROS	PIK3CA-related overgrowth spectrum
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SDS	Standard Deviation Scores

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CBYL719F12002, a retrospective chart review study of patients with PIK3CA-Related Overgrowth Spectrum (PROS) who have received alpelisib as part of a compassionate use program. The content of this SAP is based on protocol CBYL719F12002 v1.0.

All decisions regarding final analysis, as defined in the present Statistical Analysis Plan (SAP) document, have been made prior to date of data abstraction.

1.1 Background and rationale

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 and hypertriglyceridemia (https://lipidworld.biomedcentral.com/articles).

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 xenograph 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 was improved, and hemihypertrophy and scoliosis was 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 medical charts into the study database.

Novartis is supporting compassionate use requests to allow 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 so far 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.

1.2 Study objectives

Primary objective

To describe the efficacy of alpelisib as measured by the proportion of patients with response (yes/no) at Week 24 or 6 months (+/- 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.

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, 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

1.3 Study design and settings

This study will be a site-based retrospective non-interventional medical chart review of pediatric and adult male and female patients with PROS.

Patients with PROS who have received at least one dose of alpelisib initiated at least 24 weeks before the cutoff date (09-Mar-2020) through a Novartis Managed access program (MAP) and satisfy the study inclusion criteria will be included in the study.

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. Informed consent will be obtained prior to data abstraction, as appropriate, for eligible patients interested in participating in the study where required.

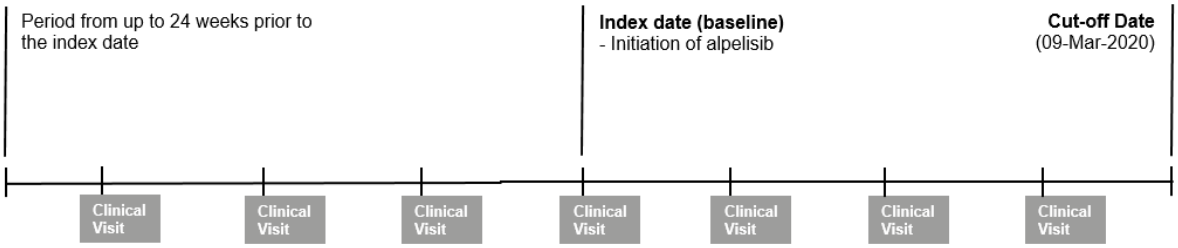
The cut-off date of 09-Mar-2020 is selected to minimize the impact of the COVID-19 pandemic on the data integrity. Eligible patients who were initiated alpelisib on or before 23-Sep-2019 are expected to have 24 weeks of relevant assessments on or before 09-Mar-2020. At that time of the cut-off, COVID-19 pandemic did not have major consequences on the regular management of the patients in the countries participating in the MAP.

The **study period** will be defined as the period from the index date up the cut-off date (09-Mar-2020) (Figure 1-1). During the study period all available data will be collected, if a patient has discontinued treatment prior to the cut-off date only data reported up to 30 days after the last date of study treatment will be abstracted and entered into the database.

The **index date (baseline)** will be defined as the date of alpelisib initiation. This date will be used as reference date for all assessments (safety and efficacy).

The **pre-index date** period will be defined as the period from up to 24 weeks prior to the index date (baseline) through to the day prior to the index date. (Figure 1-1).

Figure 1-1 Study design



Lesion assessments and definition

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 24 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.

Definition of target lesion

In the medical record, it is anticipated that measurable target lesions have already been selected by the treating physician based on the clinical/functional impact of such lesions. The clinical/functional impact will be associated with at least one of the following: patient's complaints, clinical symptoms, impaired organ function, 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)

Target lesions will be determined by the local investigator and shared with the central reviewer using available images from index date prior to any assessment of images from later in the study period. If the central review team disagrees with the local investigator’s target lesion selection, adjudication will occur.

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 selected as target and may be measured at radiologic assessment (including small lesions less than 2 cm 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 (for example, superficial visual lesions, masses, organomegaly, PROS-related enlargement of anatomic area identified by physical exam that is not measurable by reproducible imaging technique)
- Definition of new lesion will be detailed in the in the Independent Central Review Charter.

2 Changes to the protocol specified analysis

The following update on time windows were implemented following outcome of internal audit conducted in early Jan 2021.

The time window was extended for the baseline imaging scans to include imaging scans performed up to 24 weeks prior to index date, instead of 12 weeks as indicated in the protocol, to allow for flexibility given the retrospective/real world nature of the EPIK-P1 study. The extension to the time window is intended to reflect the majority of the local medical practice and to include the maximum number of patients for the primary analysis. Furthermore, the extension to the time window is unlikely to modify the baseline assessment significantly as there is not published evidence that the disease may spontaneously improve.

The time window was extended for the 24 weeks scan to include imaging scan assessments between 20 weeks and 31 weeks for the primary endpoint as well as other endpoints, instead of 20 to 28 weeks as reported in the protocol. In accordance with clinical practice in the real world setting, some physicians conducted the imaging scan assessments at 6 months (corresponding to ~ 27 weeks). As such the time window was extended (24 weeks or 6 months +/-4 weeks) to estimate the 24 week endpoints efficiently.

3 Data analysis information

3.1 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. Physician narratives will also be generated based on information recorded in the patients' medical charts and will be entered in the eCRF.

A CRF completion guide will be developed and training related to data entry will be completed for each site personnel, so that chart abstraction for the eCRF is conducted in accordance with the study protocol. A detailed data monitoring document will be developed and data will be reviewed with queries raised through the EDC platform for each site to address.

Information entered into the eCRF will be linked to available MRI scans, CT scans, clinical photographs, or clinical videos using a unique study patient ID. The unique patient ID will be automatically generated.

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

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.

3.2 Analysis population(s)

The **full study population** will include all patients that satisfy the study inclusion criteria. This population set will be used for all secondary [redacted] efficacy analyses and for safety analyses.

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 24 weeks prior to the index date) for at least one target lesion

3.3 Key post index date time points for reporting endpoint over time.

Considering the retrospective nature of the study, patients might have data available at different time-points. In order to maximize the use of data abstracted, key time points and associated time windows are identified for reporting purpose. For each of these time-points or intervals all patients with data available will be used. The total number of patients in a time interval will be equal to the number of patients with at least one valid assessment in that specific time window. The number of patients (N) in each interval will be summarized in the disposition table and used throughout the report. Only the time points with data available for at least 10% of the patients will be displayed in the corresponding output.

Key study time points are summarized in Table 3-1.

Table 3-1 Time windows for post-index date key-time point

Key time-points	Allowed windows
4 weeks	Up to 10 weeks
12 weeks	[10 to 20 weeks[
24 weeks*	[20 to 32 weeks[
36 weeks	[32 to 40 weeks[
52 weeks	[40 to 58 weeks[
End of study	4 weeks prior to and up to min(study treatment discontinuation + 30 days, cut-off date)

* 24 weeks or 6 months (+/- 4 weeks).

After week 52 intervals of approximately 11 weeks (e.g. 63 weeks, 74 weeks, etc.) with a time window of +/- 5 weeks will be used until the "end of study".

Week 24 windows (+/- 4 weeks) is intended to include assessments performed 24 weeks or 6 months after index date, where 6 months is approximated to week 27.

The last interval, referred to as “end of study” in Table 3-1, 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 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”).

In instances where more than one measure is reported in the time window associated with a key time-point (e.g., at 12 weeks), the measurement taken closest to the key-time point will be considered in the analysis. If two measures were taken on dates that are equidistant from the key time-point (e.g., 12 weeks - 5 days and 12 weeks + 5 days following the index date), the measure associated with a more severe condition (e.g., larger non-target lesion volume, higher pain severity score, lower functional assessment score) will be considered.

In instances where both a non-missing value and a missing or unknown value are reported in the time window associated with a key time-point, only the non-missing value will be considered in the analysis.

Similar rules applies to the volumetric measurement available for the patients.

If a patient has more than one volumetric measurement available for a single target lesion in the time window associated with the index date (i.e., up to 24 weeks prior to the index date) or at 24 weeks (i.e., ± 4 weeks) following the index date, the measurement taken closest to the index date or 24 weeks following the index date will be considered in the analysis. If two volumetric measurements for a single target lesion were taken on dates that are equidistant from the index date or 24 weeks following the index date, the larger of the two measurements (i.e., greatest volume) will be considered. All measurements available will be listed.

Imputation rules for the dates are reported in the Appendix.

3.4 Patient disposition, demographics and other baseline characteristics

Patient disposition

All patients in the MAP will be screened to identify the eligible patients and the number (%) of patients included in the Full study population set will be presented. The number (%) of patients in the Full study population who are still on treatment at the time of the cutoff date, patients who discontinued and the reason for discontinuation will be presented overall and at key time-points.

The number (%) of patients in each analysis set (defined in Section 3.2) will be summarized overall and at key time-points.

Protocol deviation summaries

The number and percentage of patients in the Full study population with any protocol deviation will be summarized by deviation category. All protocol deviations will be listed.

Demographic and clinical characteristics at index date

All demographic and clinical characteristics information collected at index date and during the pre-index period will be summarized and listed based on the full population set.

Descriptive analyses will be conducted where categorical data (e.g. sex, age groups, ethnicity, PRO subtype, PI3KCA mutation, mosaicism proportion, presence/absence of target and non-target lesions, site of lesions) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data at index date will be provided. Continuous

data (e.g. age, number of lesions) will be summarized by descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum and maximum).

Non-medical resource use (e.g., physical therapy, occupational therapy, home care services), frequency of hospitalizations and ER visits, proportion of patients receiving prior PROS-related medication during the pre-index period will be summarized and listed. Prior PROS medications and PROS-related surgical/vascular interventions will be reported since diagnosis, where available.

Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history, comorbidities and current medical conditions 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 MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

All other data collected during the pre-index period and at index date will be listed based on their availability.

3.5 Primary endpoint

The primary endpoint will be the proportion of patients with response (yes/no) at Week 24 or 6 months (+/- 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. The primary endpoint measure is summarized in Table 3-2 .

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 or 6 months for which the volumetric measurement cannot be calculated are defined as non-responders.

The primary analysis will be performed on all patients in the efficacy population without missing response (complete case analysis).

3.5.1 Definition of response

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

- Patient achieved ≥ 20% reduction from index date (or up to 24 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 or 6 months (+/- 4 weeks) following the index date
- None of the individual target lesions has ≥ 20% increase from index date to Week 24 o 6 months (+/- 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 or 6 months (+/- 4 weeks)
- No appearance of new lesions at Week 24 or 6 months (+/- 4 weeks)

Patients will be defined as non-responders if they meet at least one of the following criteria:

- Patient achieved < 20% reduction from index date (or up to 24 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 or 6 months (+/- 4 weeks) following the index date
- Any of the individual target lesions has ≥ 20% increase from index date to Week 24 or 6 months (+/- 4 weeks)
- Patient permanently discontinue alpelisib prior to 24 weeks of treatment
- Patient require surgery as rescue therapy between index date and 24 weeks of treatment with alpelisib due to disease deterioration.
- Progression of non-target lesions at week 24 or 6 months (+/- 4 weeks)
- Appearance of new lesion at week 24 or 6 months (+/- 4 weeks)
- Patients with MRI scan performed at week 24 or 6 months (+/- 4 weeks) for which the volumetric measurement of the selected target lesions (1 to 3 lesions, via central radiological assessment) cannot be calculated.

Patients will be considered as having a missing response if lesion volume(s) assessment at 24 weeks or 6 months (+/- 4 weeks) following the index date is not available and:

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

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

Surgery as rescue therapy is considered as required due to worsening of any existing lesions or development of a new lesions requiring intervention while on alpelisib treatment.

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.

Progression based on non-target and new lesions will be based on radiological assessment of the central reader.

In relation to non-target lesions, progression will be assessed for the lesions that are identified at index date (or up to 24 weeks prior) with available information at Week 24 or 6 months (+/- 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.

Evaluation of radiographic response and progression of all measurable lesions (target and non-target) will be provide to Novartis by a third party vendor. All details are summarized in the Independent Central Review Charter (ICRC).

[redacted]

Table 3-3 Primary endpoint measure

Measure	Type of variable	Statistics	Time point for reporting
Proportion of patients with response at Week 24 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	Binary	n, missing, frequency, percentage, 95% CI	At 24 weeks (6 months)

The primary analysis for this study will be descriptive in nature (estimation based), and therefore no hypothesis testing will be conducted. Categorical and binary data will be presented by frequency counts and percentages. The Clopper-Pearson exact method will be used to estimate 95% CIs for binary data.

3.5.2 Handling of missing data for the primary endpoint

As this is a retrospective, non-interventional study, information may not be systematically collected at each time-point of interest, resulting in missing data.

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 completeness of the response variable will be enumerated by reporting the following:

- Reasons for missing response at week 24 or 6 months (+/- 4 weeks), including missing imaging scans, as available (e.g., insurance considerations, age considerations, absence of overgrowth, differences in clinical practice) where available will be reported.
- Differences in the patient population with regard to demographic and clinical characteristics (e.g., age, PROS sub-type) will be reported in a table for patients with and without 24 weeks or 6 months (+/- 4 weeks) assessments.

For the primary endpoint, 1 to 3 target lesions identified at index date via central review of imaging scans are considered. If information about volumetric assessment of one or two identified target lesions at index date is missing/non-evaluable at Week 24 time point (24 weeks or 6 months (+/- 4 weeks)) , the sum of target lesions volume will be calculated using only the target lesion with paired assessment available.

3.5.3 Sensitivity and supportive/supplemental analyses

Supportive analyses reported in this section are targeted to investigate the robustness of the primary analysis, to model assumptions and data limitations using the efficacy population.

Sensitivity Analysis 1

Clinical practice, including frequency of monitoring patients with PROS is highly variable, and it is anticipated that imaging data may not be available at every key time point during the study period. Based on site feasibility discussions, the variability in frequency of imaging are due to the following reasons: individualized monitoring based on patient-specific needs or age; that

imaging may not be necessary/useful to monitor patient response; institution and insurance policies may not allow for frequent imaging.

Therefore a sensitivity analysis will be performed where missing volumetric assessments at week 24 will be multiply imputed for patients with missing response.

Multiple imputation (MI) is a simulation-based approach where missing values are replaced from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These complete data sets can then be analyzed using standard methods and software for balanced data. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty. Missing values for the change from index date in the sum of measurable target lesion volume will be imputed simultaneously based on an underlying joint normal distribution. The imputation model will include the longitudinal volumetric measurements (i.e. the MRI scans at index date and at other available time points), as well as covariates such as age, country and PROS lesion type. The number of imputations will be set to 100, the seed for the random function will be set to 45712002 (457<studycode>).

For each patient, the response status will be determined and for each imputed data set the proportion of patients with response will be calculated. The proportions of patients with response for each imputed data set will then be combined into an overall estimate using Rubin's rules (Little and Rubin 2002). The SAS procedures MI and MIANALYZE will be used to generate the multiple imputed data sets and to combine the results, respectively.

Sensitivity Analysis 2

The following sensitivity analyses for the primary endpoint will be performed by imputing best and worst case as outlined below:

- Patients with missing response (definition in section 3.5.1) at 24 weeks or 6 months (+/- 4 weeks) will be considered as "responder".
- Patients with missing response (definition in section 3.5.1) at 24 weeks or 6 months (+/- 4 weeks) will be considered as "non-responder".

3.5.4 Subgroup analyses for the primary endpoint

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

- Age (e.g., 2-5; 6-11;12-17; 18+; pediatric patients and adults patients)
- Sex
- Mutation type (e.g., frequent, less frequent)
- PROS subtype (e.g., CLOVES, KTS)
- Lesion type (e.g., vascular, adipose)

Forest plots (Response %, 95% CI) will be produced to graphically depict the treatment effect estimates in different subgroups.

3.6 Secondary endpoints

Secondary endpoints will be used to support the efficacy of alpelisib, to provide a more complete description of the impact of alpelisib on the heterogeneous manifestations of PROS and to evaluate the safety and tolerability of alpelisib.

All the secondary endpoints including the safety analysis will be reported using the full population, to analyze data over time all available data will be used (Section 3.6.2). No imputation methods will be performed.

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 (or up to 24 weeks prior) and key time-points following the index date.

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 (or up to 24 weeks prior) and key time-points following the index date.

Endpoint #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 24weeks prior) and key time-points following the index date.

In order to comprehensively demonstrate the efficacy of alpelisib treatment on target lesions, the percent change will be evaluated and reported at predefined time points throughout the study period (Section 3.3), under the assumption that a considerable number of patients have been treated for longer than 24 weeks.

Similarly as endpoint #1, the change in all measurable lesions, including the non-target, need to be assessed to confirm the potential benefit of alpelisib.

The percent change in the sum of measurable lesion volume (target and non-target) for each patient from index date to a generic key time point X (with X = 4, 12, 24, 36, 52 etc), will be calculated using the following equation:

$$\frac{Sum(volume1_{Xweeks},\ volume2_{Xweeks}, volume3_{Xweeks}) - Sum(volume1_{index},\ volume2_{index}, volume3_{index})}{Sum(volume1_{index},\ volume2_{index}, volume3_{index})}\ x\ 100\%$$

The change and percent change in lesion volume will be assessed as a continuous measure over time. A graphical representation, such as box plots at each time-point, will be provided to illustrate changes over time. A by patient graph will also be considered to depict individual trend. Additional information on time windows for each study key-time point following the index date are reported in Section 3.3.

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

Duration of response (DOR) is defined as the time from first documented response, to the date of the first documented disease progression or death due to any cause. This analysis only applies to responders (definition Section 3.5). The start date is the date of first documented

response, and the end date is defined as the date of the first documented disease progression or death due any cause. Patients continuing without event will be censored at the date of their last adequate lesion assessment (i.e. MRI scans performed to assess volumetric measurements).

DOR will be listed and summarized for all patients in the efficacy set with response. 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 only if a sufficient number of responses is observed.

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

This endpoint will assess the alpelisib exposure pattern in the study population, including any treatment interruption, dose changes and duration of treatment overall during the study period. The number of patients who have at least one dose adjustment, interruption, or discontinuation, and their reasons will be reported where available.

Furthermore, the concomitant utilization of PROS-related medications, such as those prophylactic antibiotics, pain medications and anti-epileptics, as well as PROS-related non-drug treatments, such as ketogenic diets and surgical corsets, will allow to establish an association between the efficacy of alpelisib (as measured by the primary end point) and symptomatic/clinical benefit for the patient.

Concomitant medications (other than alpelisib) include medications starting on or after the index date or medications starting prior to the index date and continuing after index date. Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages.

Duration of alpelisib exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by age. The number of patients with dose reductions/interruptions, and the reasons, will be summarized and listed.

Duration of exposure to alpelisib defined as follow:

Duration of exposure (days) = (last date of know exposure to alpelisib) – (index date) + 1.

The last date of exposure is the last date when a nonzero dose of study drug is administered and recorded in the (e)CRF. For patients who are still receiving treatment at the time of cut-off date, the cut-off date will be used as last exposure date. The duration of exposure includes the periods of temporary interruption.

Summary of duration of exposure of alpelisib will include categorical and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time (months).

Cumulative dose is defined as the total dose of the alpelisib given during the study. Cumulative dose will be summarized using descriptive statistics.

Dose intensity (DI) is defined as: DI (mg/day) = Cumulative dose (mg) / Duration of exposure (days).

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients; at the start of treatment; generically 250 mg for adults and dose of 50 mg for pediatric patients are used per day.

Relative dose intensity (RDI) is defined as: RDI (%) = DI (mg/day) / PDI (mg/day) *100

The number (%) of patients with dose reductions or interruptions and permanent discontinuations, and associated reasons, will be summarized.

For alpelisib a dose reduction is defined as a decrease in dose from the starting dose (e.g. from 250 mg daily to 200 mg daily) even if the dose decrease has been directly preceded by an interruption. On the other hand, if the dose decrease is followed by an interruption, with the dose resuming at the same level prior to the interruption (e.g. in the sequence 250 mg daily – 0 mg - 250 mg daily), the second dose decrease or change in dosing frequency will not be counted as dose reduction.

An interruption is defined as a zero dose on one or more days between two non-zero doses.

A dose increase is defined as an increase as compared to the starting dose level. Note that a dose rechallenge i.e when a patient goes back to the previous prescribed dose after an interruption, is not considered as an increase.

Table 3-4 Endpoints related to objective #5

Measure	Type of variable	Summary Statistics	Timing
Duration of exposure to alpelisib	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Alpelisib average daily dose; cumulative dose; dose intensity; relative dose intensity	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Proportion of patients that discontinued alpelisib	Binary	Frequency, percentage	Overall during study period;
Reason for discontinuation of alpelisib	Categorical	Frequency, percentage	Overall during study period;
Proportion of patients with an alpelisib dose adjustment	Binary	Frequency, percentage	Overall during study period
Proportion of patients with an alpelisib dose interruption	Binary	Frequency, percentage	Overall during study period
Reason for alpelisib dose interruption	Categorical	Frequency, percentage	Overall during study period

Measure	Type of variable	Summary Statistics	Timing
Number of alpelisib dose interruptions and/ or discontinuations	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Proportion of patients receiving PROS-related medication	Binary	Frequency, percentage	Overall during study period; At key time points
Indication of treatment for PROS-related medication	Categorical	Frequency, percentage	Overall during study period; At key time points
Proportion of patients receiving non-drug treatment by type (e.g., feeding tube, ketogenic diet)	Categorical	Frequency, percentage	Overall during study period;
Proportion of patients receiving non-drug treatment	Binary	Frequency, percentage,	Overall during study period ;
Reasons for discontinuation of non-drug treatment (e.g., lack of efficacy, preparation for medical procedure)	Categorical	Frequency, percentage	Overall during study period;
Proportion of patients with surgery	Binary	Frequency, percentage	Overall during study period
Proportion of patients with surgery by type (e.g., amputation, debulking, scoliosis, epiphysiodesis)	Categorical	Frequency, percentage	Overall during study period
Number of surgeries	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period

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

The following endpoints are included to establish an association between the efficacy of alpelisib (as measured by the primary endpoint) and any improvement seen on the symptoms and complications experienced by the patient.

PROS symptoms and complications between the index date and key time-points following the index date (Table 3-1) will be reported.

Type of PROS symptoms and complications and comorbidities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings. Summaries will be presented by primary system organ class (SOC) and preferred term (PT). Severity as defined by the investigator and directly abstracted in the CRF will also be summarized. Results may be also reported graphically.

Moreover, the same measure will be assessed, as available, for the pre-index period and reported separately, to describe the symptoms and complications experienced by the patient before starting alpelisib.

Results of a questionnaire recording pain severity (i.e. Wong Baker, FLACC and Numerical scale rating) will be summarized at the index date and the proportion of patients with "improvement", "worsening" and "stable" will be reported at 12 weeks, 24 weeks or 6 months, 52 weeks and at the "End of study", all other time points will be listed.

For the Wong Baker scale, "improvement" is defined as a decrease by at least 2 points and worsening is defined as an increase by at least 2 points. For the FLACC and the Numerical scales, an "improvement" is defined as a decrease by at least 1 point and worsening is defined as an increase by at least 1 point. Results from other scales will be listed, if reported.

To further assess pain reduction at week 24 time point the following items will be summarized at index date and between week 24 or 6 months (+/- 4 weeks): concomitant medications used for pain excluding opioids; opioids; medical conditions/treatment emergent adverse events (by grade) related to pain; pain score from the questionnaire. A pain reduction will be flagged if improvement is reported for at least one of the following items provided that none of the other items is associated with a deterioration during the same period: pain score from the questionnaire, number of concomitant medications excluding opioids, number of opioids, number and severity of pain related medical conditions/treatment emergent adverse events.

To identify concomitant medications used for pain the following ATC will be selected:

1. M02 "TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN";
2. M03 "MUSCLE RELAXANTS";
3. N02 "ANALGESICS";
4. V10B PAIN PALLIATION";
5. M09AB01 "chymopapain".

To identify concomitant opioids used for pain the ATC code N02A "Opioids" will be used.

Current medical conditions/adverse events related to pain will be identified by selecting all Preferred Terms (PT) related to pain. The list of PT used to select pain will be identified by the clinical team and archived.

Table 3-5 Endpoints related to objective #6

Measure	Type of variable	Summary Statistics	Timing
Proportion of patients with symptom/complication/comorbidity overall and by severity	Binary	Frequency, percentage	At key time-points
Type of symptom/complication overall and by severity	Categorical	Frequency, percentage	At key time-points
Proportion of patients with "High", "Medium" and "Low" impact symptoms/complications/comorbidities adverse events (see definition in section 3.6 Secondary endpoints) by primary	Categorical	Frequency, percentage	Overall

Measure	Type of variable	Summary Statistics	Timing
system organ class (SOC) and preferred term (PT)			
Proportion of patients with a pain assessment performed	Binary	Frequency, percentage	At index date
Proportion of patients with improvement, worsening and stable in pain severity	Binary	Frequency, percentage	At key time-points
Pain reduction (indicator)	Binary	Frequency, percentage	At week 24 time-point

Endpoints related to secondary objective #7: Change in functional status

The following endpoints are included for analysis to describe any improvement in PROS patients being able to return to, or improve their attendance at work/school, as well as any change in their ability to undertake usual activities of daily living, such as improvements in mobility. It is anticipated that the data availability associated with these endpoints may not be consistent across all patients/sites; however it will be reported as available and utilized also to generate physician narratives.

The number of patients attending work/school/pre-school will be summarized at the index date and the percentage of patients reporting improvement, worsening or stable at each time-point will be reported. The reason for change of status will be listed where available.

Frequency counts and percentages will be presented for mobility assessments at the index date and at key time-points. Performance status scores (ECOG, Lansky, Karnofsky) will be reported appropriately by age category, at the index date and the percentage of patients reporting improvement, worsening or stable in score will be summarized at baseline, 12, 24 and 52 weeks windows as well as the "End of study".

For work attendance:

- "Improvement" is defined as a shift from reporting of "No attendance" to "Part-time" or "Full time", from "Part-time to "Full-time", as well as from "Unemployed" to "Part-time" or "Full-time" work.
- "Worsening" is defined as a shift from reporting of "Part-time" to "No attendance", "Full-time" to "Part-time" or "No attendance" as well as "Part-time" or "Full-time" to "Unemployed" status.

Similarly, for school attendance:

- "Improvement" is defined as a shift from reporting of "No attendance" to "Part-time" as well as , "Part-time" or "No attendance" to "Full-time";
- "Worsening" is defined as a shift from reporting of "Part-time" to "No attendance", as well as from "Full-time" to "Part-time" or "No attendance".

Work attendance will only be reported for the adult patients (i.e., ≥18 years of age) while school attendance will be reported for both pediatric and adult patients

For the ECOG scale, "improvement" is defined as a decrease by at least 1 point and "worsening" is defined as an increase by at least 1 point. For the Karnofsky and Lansky scale, "improvement" is defined as an increase by at least 20 points and worsening is defined as a decrease by at least 20 points. For example if a patient reports a score of 100 ("Normal, no complaints") at index date and a score of 80 ("Care for self. Unable to carry on normal activity or to do active work") would be considered as "worsening" while a score of 90 will still be considered as "stable". This approach takes into account the criteria for correspondence between the ECOG and Karnofsky/Lansky scale to make the categorization comparable and consistent between the scales. Results from other scales will be listed, if reported.

Importantly, based on feasibility discussions with study sites, it is anticipated that there will be variability in the use of the listed performance status measurement tools, based on preference of each institution, as well as variability on whether a performance measure is utilized for each patient (given the heterogeneity in the complications experienced by PROS patients).

Table 3-6 Endpoints related to objective #7

Measure	Type of variable	Summary Statistics	Timing
Proportion of patients that attend work/school/pre-school, overall and by type (i.e., full-time, part-time, no attendance)	Categorical	Frequency, percentage	At index date
Proportion of patients with "improvement", "worsening" and "stable" in work/school/pre-school attendance	Categorical	Frequency, percentage	At key time-points
Proportion of patients with any mobility assessments	Binary	Frequency, percentage	At key time-points
Severity of mobility impairment (i.e., no, mild, moderate, severe, total impairment)	Categorical	Frequency, percentage	At key time-points
Proportion of patients with a functional assessment (i.e., ECOG, Karnofsky, Lansky, other) performed	Binary	Frequency, percentage	At index date
Functional assessment score (ECOG, Karnofsky, Lansky)	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	At index date
Proportion of patients with "improvement", "worsening" and "stable" in functional assessment (ECOG, Karnofsky, Lansky)	Binary	Frequency, percentage	At key time-points

Endpoints related to secondary objective #8: Change in Healthcare resource use (HRU)

An important aspect of treatment with alpelisib consist in the healthcare resources needed to care for patients with PROS. The necessity for frequent hospitalization and ER visits could have both an economic and a general health impact on PROS patients. The analyses below aims to describe the pattern observed in the study population.

The proportion of patients using non-medical resource, hospitals and ER visits will be reported, along with the relation to the disease, during the study period.

Moreover the same measure will be assessed as available for the pre-index period and reported separately, to assess the use of HRU and ER visits prior to start of alpelisib.

Table 3-7 Endpoints related to objective #8.

Measure	Type of variable	Summary Statistics	Timing
Proportion of patients using non-medical resource (e.g., physical therapy, occupational therapy, home school)	Binary	Frequency, percentage	Overall during study period
Proportion of patients using non-medical resource due to PROS (i.e., related or not related)	Binary	Frequency, percentage	Overall during study period
Frequency of non-medical resource use	Categorical	Frequency, percentage	Overall during study period
Proportion of patients with ≥ 1 hospitalization	Binary	Frequency, percentage	Overall during study period
Proportion of patients with ≥ 1 hospitalization related to PROS (i.e., related or not related)	Binary	Frequency, percentage	Overall during study period
Number of hospitalizations	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Number of hospitalizations related to PROS	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Duration of hospitalizations	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Duration of hospitalizations related to PROS	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Proportion of patients with ≥ 1 ER visit	Binary	Frequency, percentage	Overall during study period
Proportion of patients with ≥ 1 ER visit related to PROS (i.e., related or not related)	Binary	Frequency, percentage	Overall during study period
Number of ER visits	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period
Number of ER visits related to PROS	Continuous	N, mean, median, standard deviation, Q1, Q3, minimum and maximum	Overall during study period

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

The following endpoints will assess changes in patient's clinical assessments cardiac (e.g., ECG, BNP) and laboratory assessments (e.g., D-dimer, fibrinogen, hemoglobin) as well as vital signs (e.g., height, weight, blood pressure, pulse oximetry) between the index date and key time-points following the index date, appropriately by age groups.

The following summaries will be produced for laboratory data (by laboratory parameter):

- Worst post-baseline Common Toxicity Criteria (CTC) grade. Each patient will be counted only for the worst grade observed during study period.
- Shift tables using CTC grades to compare index date to the worst collected value during study period.
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare index date to the worst collected value during study period.

Vital signs assessments are reported in order to characterize basic body function. The parameters expected to be collected may include: height, weight, respiratory rate, systolic and diastolic blood pressure. The number and percentage of patients with notable vital sign values (high/low) will be presented. A listing of all vital sign assessments will be produced and notable values will be flagged.

Clinically notable vital sign criteria are provided Table 3-8 below.

Table 3-8 Clinically notable changes in vital signs

Vital sign		Patient age at visit	
		< 18 years	**≥ 18 years**
Systolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]	≥ 180 with increase from updated baseline[5] of ≥20 mmHg
	Low	≤ 5th percentile of the age and height group[1]	≤ 90 with decrease from updated baseline[5] of ≥20 mmHg
Diastolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]	≥ 105 with increase from updated baseline[5] of ≥15 mmHg
	Low	≤ 5th percentile of the age and height group[1]	≤ 50 with decrease from updated baseline[5] of ≥15 mmHg
Oral body temperature [°C]	High	≥ 38.4°C	≥ 39.1°C
	Low	≤ 35.0°C	
Pulse rate [bpm] [2]	High		
		2-3 years	> 128
		3-4 years	> 123

Vital sign		Patient age at visit		
		< 18 years		**≥ 18 years**
		4-6 years	> 117	≥120 with increase from updated baseline[5] of ≥15 bpm
		6-8 years	> 111	
		8-12 years	> 103	
		12-15 years	> 96	
		≥ 15 years	> 92	
	Low			
		2-3 years	< 92	≤50 with decrease from updated baseline[5] of ≥15 bpm
		3-4 years	< 86	
		4-6 years	< 81	
		6-8 years	< 74	
		8-12 years	< 67	
		12-15 years	< 62	
		≥ 15 years	< 58	
Weight	High	increase from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]		Weight increase from updated baseline[5] of ≥ 10%
	Low	decrease from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]		Weight decrease from updated baseline[5] of ≥ 10%
Respiratory rate [breath per minute][2,6,7]	High			
		2-3 years	> 34	≥30bpm
		3-4 years	> 29	
		4-6 years	> 27	
		6-8 years	> 24	
		8-12 years	> 22	
		12-15 years	> 21	
		≥ 15 years	> 20	
	Low	2-3 years	< 22	≤ 10bpm
		3-4 years	< 21	
		4-6 years	< 20	
		6-8 years	< 18	
		8-12 years	< 16	
		12-15 years	< 15	
		15-18 years	< 13	

bpm=beats per minute; NHLBI= National Heart, Lung, and Blood Institute;

[1] Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

Vital sign	Patient age at visit	
	< 18 years	≥ 18 years

[3] Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile);

[4] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/);

[5] Updated baseline is the last value collected before the 18th birthday.

[6] Eldridge L. What is a Normal Respiratory Rate?, Updated May 16, 2014;

[7] Kou .R., Shuei L., Bradypnea, Department of Physiology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, http://rd.springer.com/referenceworkentry/10.1007%2F978-3-540-29676-8_246

Growth and development will only be summarized for patients who were aged <18 years at the time of alpelisib initiation.

BMI (kg/m2) will be calculated as weight [kg] / (height2 [m2]). Individual trajectories for height and BMI will be compared to growth standards from the World Health Organization. Data are available online at (http://www.who.int/childgrowth/en/). Height and BMI will be summarized through the standard deviation score (SD- score), velocity and velocity SDS.

Z-scores or SD- scores are used to describe how far a measurement is from the median (average). The distribution of heights of all boys (or all girls) of a certain age follows a normal (or almost normal) distribution. The z-score of an observed point in this distribution is calculated as follows: Z-score (or SD-score) = (observed value - median value of the reference population) / standard deviation value of reference population. These scores are calculated differently for measurements that are distributed normally and non-normally in the reference population (Interpreting growth indicator, WHO. https://www.who.int/childgrowth/training/module_c_interpreting_indicators.pdf?ua=1)

Height and BMI SDS will be summarized using descriptive statistics (mean, standard deviation, range), as well as by presenting number of patients with SDS values lower/higher than 5th/95th percentiles respectively. Shift tables will be provided to compare index date to the last available value recorded during study period. Box plots may also be plotted for each time window.

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*)

÷ ([assessment date in time window *k* – assessment date in time window *k-1*] ÷ [365.25/2]),

and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / SD, where mean and SD are obtained as the height-, weight-, sex- and age-specific values in Tables 5 to 8 in Baumgartner et al (1986), where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

Height/weight SDS and velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window, as well as by presenting number of patients with SDS values lower/higher than $5^{th}/95^{th}$ percentiles respectively. Box plots will also be plotted for key time points.

Endpoint #10: Type, frequency, seriousness, and severity criteria and causality assessments of treatment-emergent adverse events.

Adverse events summary tables will report only on-treatment assessments/events (more details in Appendix). An on-treatment adverse event is defined as any adverse event reported in the following time interval (including the lower and upper limits):

- date of first administration of study treatment; date of last administration of study treatment + 30 days or cut-off date whichever occurs first

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. The full population will be used for reporting Adverse Events (AE) and all safety endpoints. As much as possible, each AE will be evaluated to determine:

- Toxicity grade
- Impact ("Low", "Medium" and "High")
- Duration
- Relationship to the study treatment (i.e., not related, related, unknown)
- Whether it is serious as per medical chart
- Action taken with respect to study treatment (i.e. dose increased; dose not changed; dose reduced; drug interrupted; drug withdrawn). If a concomitant medication or additional therapy was provided (for example diet for impaired glycemic control)
- Outcome (i.e., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc.

AEs will be summarized by number and percentage of patients having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades (version v4.03) for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

CTC grading of AE may be missing for a proportion of AE as information was not collected and retrospective assignment of a grade may not be feasible precluding a comprehensive assessment of the safety profile.

A proxy variable called "impact" will be derived using all available information on each AE/medical condition and will integrate the Important Medical Event Terms (IME) list.

The EudraVigilance Expert Working Group (EV-EWG) coordinated the development of an Important Medical Event Terms (IME) list. This IME list is used by the EMA and other European regulators to facilitate the classification of suspected adverse reactions.

The list identifies MedDRA Preferred Terms (PTs) and the criteria for selection were based on the official ICH definition of seriousness.

"High" impact is defined as satisfying one of the following conditions:

- Reported as ≥Grade 3 (regardless of seriousness)
- Or reported as serious (regardless of grading)
- Or leading to dose discontinuation (regardless of grading)
- Or MedDRA Preferred Terms (PTs) reported in the IME list.

"Medium" impact is defined as an event that does not belong to "High" and satisfies one of the following conditions:

- Reported as Grade 2 (not serious)
- Or reported with a grade missing but leading to take concomitant medication and/or to alpelisib dose reduction/interruption

"Low" impact is defined as an event that does not belong to "High" or "Medium" and satisfies one of the following conditions:

- Reported as Grade 1
- Or reported with a grade missing and no action taken (i.e., no need for concomitant medications and no alpelisib dose reductions/interruption).

If an event cannot be classified into any of the above categories then it will be considered as having impact unknown.

Impact will be reported for all AEs and for medical conditions.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency.

The following adverse event summaries will be produced: overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship (all AEs and AEs judged to be related to alpelisib), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, including the duration of interruption, requiring a concomitant medication or an additional treatment.

The AE will be reported overall and by age categories, differentiating between pediatric and adult population as appropriate.

Analysis of AESIs

Specific groupings of Adverse Events of Special Interest (AESI) will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with alpelisib treatment (i.e. where alpelisib may influence a common mechanism of action responsible for triggering them) or AEs which are similar in nature (although not identical). The groups are defined according to the MedDRA terms defined in the program Case Retrieval Strategy (CRS) document and will be summarized. The latest version of the CRS document available at the time of the analyses will be used.

All AESI groupings are defined through the use of Preferred Terms (PT), High Level Terms (HLT) or System Organ Classes (SOC) or through a combination of these three components.

An Excel file with the exact composition of the AEs groupings is to be used to map reported AEs to the AESI groupings. This file is an output from electronic Case retrival Strategy (eCRS), which may be updated (i.e. it is a living document) based on review of accumulating trial data. Note that certain AEs may be reported within multiple groupings. Final deliverables will be aligned with the final eCRS version. A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

Table 3-8 List of all AESI grouping levels and related MedDRA terms

AESI groupings	MedDRA Term
Stomatitis	Stomatitis and ulceration (HLT)
Severe cutaneous reactions (AESI)	Severe cutaneous adverse reactions (SMQ)
Rash (AESI)	Rash [BYL719] (CMQ)
Pneumonitis (AESI)	Interstitial lung disease (SMQ)
Pancreatitis (AESI)	Acute pancreatitis (excl non-specific symptoms) [STANDARD] (NMQ)
Hypersensitivity and anaphylactic reaction (AESI)	Hypersensitivity [BYL719] (CMQ)
Hyperglycaemia (AESI)	Hyperglycaemia/new onset diabetes mellitus (SMQ)
GI toxicity Nausea Vomiting Diarrhea (AESI)	Nausea, vomiting, diarrhoea (Clinical) [BYL719] (CMQ)

Analysis for AESI will be conducted as follows:

- The number (%) of patients with AESI will be reported by AESI grouping, maximum CTCAE grade and by age group.
- Action taken and outcome of each AESI
- All AEs of special interest will be listed.
- Impact.

Time (days) to onset of first grade 2 or worse Hyperglycemia (based on laboratory data) will be summarized using Kaplan-Meier method. Median time to onset, duration and 95% CI will be summarized., Ascending Kaplan-Meier plots will be generated.

Time to onset of first grade X or worse toxicity is defined as the time from the start of treatment to the start date of the first incidence of grade X or worse toxicity i.e. time in days is calculated as (start date of first occurrence of grade X or worse toxicity) – (date of first dose of study treatment) +1.

In the absence of grade X or worse toxicity during the on-treatment period, the censoring date will be the earliest date from the following dates:

- last date of administration of study treatment + 30 days or last non-missing lab assessment on-treatment if the event is lab based,
- analysis cut-off date,
- death date.

Note: patients who have grade X or worse toxicity at the index date will be excluded from this analysis.

Duration of first event (days) is defined as time from onset to the date of first resolution of the event: (date of first resolution of event) - (date of onset of event) +1. Resolution of an event means that there is a lab value returning to grade ≤ 1 or back to the baseline grade for patients with an increase in grading while on treatment.

Grade 2 or worse Hyperglycaemia (laboratory data) will be analysed for time to resolution.

Duration of first event will be presented for the subset of the full population who experienced the event.

A patient will be censored for time to resolution, if there is no resolution during the on-treatment period. The same censoring rules as described in time to first onset apply for duration of first occurrence.

Failure curves (descending Kaplan-Meier curves) will be constructed. Median together with 95% confidence interval, as well as 25th percentile and 75th percentile, will be presented.

3.6.1 Statistical methods for the secondary endpoints

The secondary analyses for this study will be descriptive in nature and therefore no hypothesis testing will be performed. Descriptive analyses will be conducted where continuous data will be summarized by measures that will include the N, mean, median, standard deviation, Q1, Q3, minimum and maximum. Categorical and binary data will be presented by frequency counts and percentages.

3.6.2 Handling of missing data for the secondary endpoints

To report of the secondary endpoint all available data at that specific time point will be used. At each time point the total number of patients with available data will be shown. No imputation methods will be performed. If at the time point a parameter is missing for that patient it will not be reported.

4 Appendix

4.1 General definitions

Study treatment

The term study treatment or study drug will be used in this document and will refer to alpelisib.

Date of first administration of study drug

The date of first administration of alpelisib is defined as the first date when a non-zero dose of alpelisib is administered and recorded in the (e)CRF. This date is referred to as index date and used as reference start date.

Date of last administration of study drug

The date of last administration of alpelisib is defined as is the last date when a nonzero dose of alpelisib is administered and recorded in the (e)CRF.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of alpelisib is defined as "baseline" assessment.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into two mutually exclusive segments:

1. ***pre-index date/pre-treatment period***: from up to 24 weeks prior to the index date through to the day prior to the index date.
2. ***post-index date/on-treatment period***: from date of first administration of study treatment to 30 days after date of last administration of alpelisib (including start and stop date).

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

4.2 Statistical methods

Kaplan-Meier estimates

An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

4.3 Imputation rules

4.3.1 AE, ConMeds and safety assessment date imputation

Table 4-1 Imputation of start dates (AE, Symptoms and complications, concomitant medications medical history, health resources utilization, non-drug treatment and other medical interventions)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date (index date) then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Day	• If available month and year = month and year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  ○ Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 4-2 Imputation of end dates (AE, Symptoms and complications, concomitant medications, medical history, health resources utilization, non-drug treatment and other medical interventions)

Missing Element	**Rule** (*=earliest between (last treatment date plus 30 days, death date, cut-off date)
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the study period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the study period*
Day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the study period*

Table 4-3 Imputation of start dates for assessments (Laboratory evaluation, vital signs, ECG, growth data, medical procedure (surgery), death, questionnaires, PROS disease history)

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date (index date) then set start date = max(study treatment start date, 01JulYYYY). • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then max (01JulYYYY , Pre-Index date)
Day	○ If available month and year = month and year of study treatment start date then set start date = max(study treatment start date, 15MONYYYY). • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then max(15MONYYYY , Pre-index date)

If imputed date is before birth or after DCO, death date or study discontinuation the last will be used.

If imputed end date is earlier than the start date or of the imputed start date then the imputed end date = start date.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.
For treatment start and end date if day is missing then it will be set to be the 15th of the month and if both month and day are missing, is defaulted to 01-Jan.

Treatment end date = min (imputed treatment end date*, death date, cut-off date).
If Imputed treatment end date < Treatment start date then Treatment end date= treatment start date.

Similar imputation will be performed for similar assessment in the pre-index period, more details as will be provided in the PDS.

4.3.1.1 Imputations and study periods (pre-index, study period)

If "Start" and "End" dates are completely missing with no specification of whether the event is "Ongoing", then the event will be assumed to be happening during the study period.

If "Start" and "End" dates are both missing and "Ongoing" is specified, then the event is assumed to be happening during study period.

In case the "Start" date is completely missing but the "End" date is non- missing or partially missing:
- if end date is in the study period, then the therapy will be assigned only to the study period.
- if end date is before the index date, then the event will be assigned to the pre-index period only.

4.3.1.2 Other imputations

Partial dates

For imputation of the partial dates when not otherwise specified the following rule will apply: missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete lesion assessment dates

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the

month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.4 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version v4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version v4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

4.5 Growth Charts

https://www.who.int/tools/growth-reference-data-for-5to19-years

WHO
BMI_Height_Weight sl

5 References

Fritsch C, Huang A, Chatenay-Rivauday C, et al Characterization of the novel and specific PI3Kα inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. *Molecular cancer therapeutics.* 2014;13(5):1117–1129.

Hoste G, Slembrouck L, Jongen L, et al Unexpected benefit from alpelisib and fulvestrant in a woman with highly pre-treated ER-positive, HER2-negative PIK3CA mutant metastatic breast cancer. *Clinical drug investigation.* 2018;38(11):1071–1075.

Juric D, Janku F, Rodón J, et al Alpelisib Plus Fulvestrant in PIK3CA-Altered and PIK3CA-Wild-Type Estrogen Receptor–Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. *JAMA oncology.* 2019;5(2):e184475-e184475.

Keegan NM, Gleeson JP, Hennessy BT, Morris PG. PI3K inhibition to overcome endocrine resistance in breast cancer. *Expert opinion on investigational drugs.* 2018;27(1):1–15.

Little, R.J.A and Rubin, D.B. (2002)). Statistical Analysis with Missing Data. Wiley Series in Probabiliy and Statistics, Chapter 10.

Parker VE, Keppler-Noreuil KM, Faivre L, et al Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. *Genetics in Medicine.* 2019;21(5):1189.

van Buuren S, "Flexible Imputation of Missing Data," CRC Press (Chapman & Hall), Boca Raton, 2012. http://dx.doi.org/10.1201/b11826.

Venot Q, Blanc T, Rabia SH, Berteloot L, Ladraa S, Duong JP, Blanc E, Johnson SC, Hoguin C, Boccara O, Sarnacki S. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature*. 2018;558(7711):540.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of internal medicine.* 2007;147(8):573–577.

Interpreting growth indicator, WHO. https://www.who.int/childgrowth/training/module_c_interpreting_indicators.pdf?ua=1

Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-722.

Performances scales: Karnofsky & ECOG scores. https://oncologypro.esmo.org/oncology-in-practice/practice-tools/performance-scales

Ann Christine Catlin; Sumudinie fernando; Denise Warzel; Angela Kummerow (2014), "Performance Status Scoring : a standards portal resource," https://ncihub.org/resources/115.

IME List. EMA 2020. https://www.ema.europa.eu/en/documents/other/eudravigilance-inclusion/exclusion-criteria-important-medical-events-list_en.pdf