NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Alpelisib

Trial Indication(s)

PIK3CARelated Overgrowth Spectrum (PROS)

Protocol Number

CBYL719F12002

Protocol 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)

Clinical Trial Phase

Phase IV

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: June 2020 (Actual)
Primary Completion Date: April 2021 (Actual)
Study Completion Date: April 2021 (Actual)

Reason for Termination (If applicable)

NA

Study Design/Methodology

This study (CBYL719F12002; EPIK-P1) was a a site-based retrospective non-interventional medical chart review of patients 2 years of age and older with severe or life-threatening PROS who have received alpelisib as part of a compassionate use program (i.e. patients were treated under the ATU in France or the MAP outside of France). This study abstracted data from all eligible patients at all participating sites that had been previously recorded in the medical charts to assess the efficacy and safety of alpelisib for the treatment of the heterogeneous manifestations of PROS.
The index date (baseline) was defined as the date of alpelisib initiation. The pre-index date period was defined as the period from up to 24 weeks prior to the index date through to the day prior to the index date. The study period was defined as the period from the index date up to the cut-off date (09-Mar-2020). If a patient discontinued treatment prior to the cut-off date, only data reported up to 30 days after the last date of study treatment were abstracted and entered into the database.

During the study period, all available data were collected from the index date up to the cut-off date.

Centers

7 centers in 5 countries: France(3), Australia(1), Ireland(1), United States(1), Spain(1)

Objectives:

Primary objective

- 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 a ≥ 20% reduction from the index date in the sum of measurable target lesion volume (1 to 3 lesions, via independent central radiology review (ICRR) of imaging scans), provided that none of the individual target lesions have ≥ 20% increase from the index date and in the absence of progression of non-target lesions and without new lesions.

Secondary objectives

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

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

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of alpelisib 50 mg daily, taken with food in pediatric patients (2 to 17 years), and 250 mg daily, taken with food in adult patients (≥ 18 years).

Statistical Methods

Considering the retrospective nature of the study, patients had data available at different time-points. In order to maximize the use of data abstracted, key time points and associated time windows were identified for reporting purposes.
The analyses for this study are descriptive in nature (estimation based), and therefore no hypothesis testing was conducted. Categorical data (e.g. sex, age groups, ethnicity, PROS subtype, PIK3CA mutation, mosaicism proportion, presence/absence of target and non-target lesions, site of lesions) were summarized by frequency counts and percentages. Continuous data (e.g. age, number of lesions) are summarized by descriptive statistics (e.g. n, mean, median, standard deviation, first quartile (Q1), third quartile (Q3), and minimum and maximum).

Study Population: Key Inclusion/Exclusion Criteria

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

- Patient's condition was assessed by the treating physician as severe or life threatening and treatment was deemed necessary
- Patient has been treated with at least one dose of alpelisib, initiated on or before 23-Sep-2019 (i.e. at least 24 weeks before the cut-off date of the 09-Mar-2020)
- Patient has medical chart history available during enrollment in the Novartis MAP
- Patient (or parent/guardian in case of pediatric patient) consented to participate in the study (as required by local ethics regulations)

Inclusion criteria for MAP enrollment (assessed at the time of alpelisib initiation)

Participant Flow Table

Overall Study

	Pediatric patients	Adult patients	Total
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib	
Started	39	18	57
Completed	36	16	52
Not Completed	3	2	5
Subject decision	1	2	3
Physician Decision	1	0	1
No efficiency	1	0	1

Baseline Characteristics

	Pediatric patients	Adult patients	Total
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib	
Number of Participants [units: participants]	39	18	57
Age Continuous (units: years) Mean ± Standard Deviation			
	9.9±4.84	27.8±8.34	15.5±10.39
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	24	9	33
Male	15	9	24
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)			
Not reported	32	18	50
White	7	0	7

Primary Outcome Result(s)

Percentage of patients responders and non-responders at week 24

(Time Frame: Index date and week 24 or 6 months (± 4 weeks))

	Pediatric patients	Adult patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	23	9
Percentage of patients responders and non-responders at week 24 (units: Percentage of participants) Number (95% Confidence Interval)		
Responders	30.4 (13.2 to 52.9)	55.6 (21.2 to 86.3)
Non Responders	69.6 (47.1 to 86.8)	44.4 (13.7 to 78.8)

Secondary Outcome Result(s)

Percent change in the sum of measurable target lesion volume

(Time Frame: Index date, week 4, 12 , 24, 52 and end of study (up to a maximum of week 187))

	Pediatric patients	Adult patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	22	9

Percent change in the sum of measurable target lesion volume (units: % change in the sum of lesion vol.) Mean ± Standard Deviation		
4 weeks	-11.64 ± 12.869	-11.78 ± 8.154
12 weeks	-18.59 ± 16.837	-19.77 ± 5.128
24 weeks	-11.20 ± 19.987	-19.69 ± 15.375
52 weeks	-13.91 ± 19.206	-6.52 ± 2.614
End of study	-36.47 ± 46.137	-17.38 ± 11.679

Percent change in the sum of all measurable lesion volume

(Time Frame: Index date, week 4, 12 , 24, 52 and end of study (up to a maximum of week 187))

	Pediatric patients	**Adult patients**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	22	9
Percent change in the sum of all measurable lesion volume (units: % change in the sum of lesion vol.) Mean ± Standard Deviation		
4 weeks	-11.64 ± 12.869	-11.78 ± 8.154

12 weeks	-18.59 ± 16.837	-19.77 ± 5.128
24 weeks	-11.20 ± 19.987	-19.69 ± 15.375
52 weeks	-13.91 ± 19.206	-6.52 ± 2.614
End of study	-36.47 ± 46.137	-17.38 ± 11.679

Percent change in the sum of all measurable non-target lesion volume

(Time Frame: Index date, week 4, 12 , 24, 52 and end of study (up to a maximum of week 187))

	Pediatric Patients	**Adult patients**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	0	0
Percent change in the sum of all measurable non-target lesion volume (units: % change in the sum of lesion vol.) Mean ± Standard Deviation		

Mean duration of response (DoR)

(Time Frame: Up to 187 weeks)

	Pediatric patients	**Adult Patients**

Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	0	0
Mean duration of response (DoR) (units: Weeks) Mean ± Standard Deviation		

Reasons for discontinuation of concomitant PROS-related non-drug treatments

(Time Frame: Up to 187 weeks)

	Pediatric patients	**Adult Patients**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	31	17
Reasons for discontinuation of concomitant PROS-related non-drug treatments (units: Participants) Count of Participants (Not Applicable)		
Recovery	12 (38.71%)	2 (11.76%)
Completed the planned course of treatment	4 (12.9%)	7 (41.18%)

Unknown	2 (6.45%)	1 (5.88%)
Lack of efficacy	1 (3.23%)	1 (5.88%)
Other	2 (6.45%)	0 (%)
Adverse event	0 (%)	1 (5.88%)
Progressive disease	0 (%)	1 (5.88%)
Subject decision	0 (%)	1 (5.88%)

Participants with concomitant PROS-related medications over time

(Time Frame: Index date, week 24 and end of study)

	All Patients
Arm/Group Description	Pediatric and adult patients treated with alpelisib
Number of Participants Analyzed [units: participants]	57
Participants with concomitant PROS-related medications over time (units: Participants) Count of Participants (Not Applicable)	
Index date	34 (59.65%)
24 weeks	30 (53.57%)
End of study	25 (43.86%)

Number of PROS-related completed surgeries during the study period

(Time Frame: Up to 187 weeks)

	Pediatric Patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	39	18
Number of PROS-related completed surgeries during the study period (units: Surgeries)		
Other	4	2
Disease improvement	2	1
Disease progression (not radiologically confirmed)	3	0

Number of patients with improvement in most frequent PROS-related signs and symptoms

(Time Frame: Index date and week 24 or 6 months (± 4 weeks))

	Pediatric Patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	39	18

Number of patients with improvement in most frequent PROS-related signs and symptoms (units: Participants) Count of Participants (Not Applicable)		
Fatigue improved by week 24	22 (78.57%)	10 (71.43%)
Vascular malformation improved by week 24	20 (80%)	10 (76.92%)
Disseminated intravascular coagulation improved by week 24	11 (57.89%)	5 (50%)
Limb asymmetry improved by week 24	11 (64.71%)	9 (75%)
Pain improved by week 24	11 (91.67%)	9 (90%)

Change in performance status score

(Time Frame: Index date and week 24 or 6 months (± 4 weeks))

	Pediatric patients	**Adult patients**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	33	14
Change in performance status score (units: Participants) Count of Participants (Not Applicable)		
Stable : Stable	9 (27.27%)	1 (7.14%)

Stable : Improved	8 (24.24%)	6 (42.86%)
Stable : Worsened	0 (%)	0 (%)
Stable : Not reported	16 (48.48%)	7 (50%)

Functional status - mobility assessment

(Time Frame: Up to 187 weeks)

	Pediatric Patients	**Adult Patients**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	1	2
Number of Affected regions Analyzed	1	6
Functional status - mobility assessment (units: Affected regions) Count of Units (Not Applicable)		
mobility assessment : No impairment	0	1
mobility assessment : Mild impairment	0	1
mobility assessment : Moderate impairment	1	2
mobility assessment : Severe impairment	0	1

mobility assessment : Missing	0	1

Change from Index date in functional status - School status during the study period

(Time Frame: Index date, week 24 and end of study (up to 187 weeks))

	Pediatric patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib reporting school status	Adult patients (>= 18 years) treated with alpelisib reporting school status
Number of Participants Analyzed [units: participants]	29	4
Change from Index date in functional status - School status during the study period (units: Participants) Count of Participants (Not Applicable)		
Change 24 weeks : Improvement	1 (3.45%)	0 (%)
Change 24 weeks : Stable	28 (96.55%)	4 (100%)
Change 24 weeks : missing	0 (%)	0 (%)
Change 24 weeks : Worsening	0 (%)	0 (%)
End of study : Improvement	2 (6.9%)	2 (50%)
End of study : Stable	27 (93.1%)	2 (50%)

End of study : missing	0 (%)	0 (%)
End of study : Worsening	0 (%)	0 (%)

Change from index date in functional status - Work Status

(Time Frame: Index date, week 24 and end of study)

	Adult patients
Arm/Group Description	Adult patients (>= 18 years) treated with alpelisib reporting work status
Number of Participants Analyzed [units: participants]	8
Change from index date in functional status - Work Status (units: Participants) Count of Participants (Not Applicable)	
Change 24 weeks : Improvement	0 (%)
Change 24 weeks : Worsening	1 (12.5%)
Change 24 weeks : Stable	6 (75%)
Change 24 weeks : Missing	1 (12.5%)
Change end of study : Improvement	5 (62.5%)

Change end of study : Worsening	0 (%)
Change end of study : Stable	2 (25%)
Change end of study : Missing	1 (12.5%)

Health resource utilization (HRU) - Number of hospitalizations per patient

(Time Frame: Up to 187 weeks)

	Pediatric Patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	39	18
Health resource utilization (HRU) - Number of hospitalizations per patient (units: Number of hospitalizations) Mean ± Standard Deviation		
Number of times a patient has been hospitalized	1.8 ± 1.03	1.7 ± 0.82
Number of times a patient has been hospitalized due to PROS	1.1 ± 0.35	1.0 ± 0.00

Number of patients with grade 3/4 on laboratory assessments: Hematology

(Time Frame: Up to 187 weeks)

	Pediatric patients	Adult Patients

Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	39	18
Number of patients with grade 3/4 on laboratory assessments: Hematology (units: Participants) Count of Participants (Not Applicable)		
Activated partial thromboplastin time, increase - Grade 3/4	0 (%)	0 (%)
Fibrinogen, decrease - Grade 3/4	0 (%)	0 (%)
Hemoglobin, decrease - Grade 3/4	2 (5.13%)	1 (5.56%)
Leukocytes, increase - Grade 3/4	1 (2.56%)	0 (%)
Leukocytes, decrease - Grade 3/4	0 (%)	0 (%)
Lymphocytes, increase - Grade 3/4	0 (%)	0 (%)
Lymphocytes, decrease - Grade 3/4	0 (%)	1 (5.56%)
Neutrophils, decrease - Grade 3/4	0 (%)	1 (5.56%)
Platelets, decrease - Grade 3/4	0 (%)	1 (5.56%)

Number of patients with grade 3/4 on clinical assessments - Clinical chemistry

(Time Frame: 187 weeks)

	Pediatric Patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	39	18
Number of patients with grade 3/4 on clinical assessments - Clinical chemistry (units: Participants) Count of Participants (Not Applicable)		
Alanine Aminotransferase Increase - Grade 3/4	0 (%)	0 (%)
Albumin Decrease - Grade 3/4	0 (%)	0 (%)
Alkaline Phosphatase Increase - Grade 3/4	0 (%)	0 (%)
Aspartate Aminotransferase Increase - Grade 3/4	0 (%)	0 (%)
Bilirubin Increase - Grade 3/4	0 (%)	2 (11.11%)
Calcium Corrected Increase - Grade 3/4	0 (%)	0 (%)
Calcium Corrected Decrease - Grade 3/4	0 (%)	0 (%)
Cholesterol Increase - Grade 3/4	0 (%)	0 (%)
Creatine Kinase Increase - Grade 3/4	0 (%)	0 (%)

Creatinine Increase - Grade 3/4	0 (%)	0 (%)
Gamma Glutamyl Transferase Increase - Grade 3/4	0 (%)	0 (%)
Glucose Increase - Grade 3/4	0 (%)	1 (5.56%)
Magnesium Increase - Grade 3/4	1 (2.56%)	0 (%)
Magnesium Decrease - Grade 3/4	0 (%)	1 (5.56%)
Phosphate Decrease - Grade 3/4	0 (%)	2 (11.11%)
Potassium Increase - Grade 3/4	0 (%)	0 (%)
Potassium Decrease - Grade 3/4	0 (%)	0 (%)
Sodium Increase - Grade 3/4	0 (%)	0 (%)
Sodium Decrease - Grade 3/4	0 (%)	1 (5.56%)
Triglycerides Increase - Grade 3/4	0 (%)	0 (%)
Urate Increase - Grade 3/4	1 (2.56%)	1 (5.56%)

Notable vital sign values during the study period - Pediatric Patients

(Time Frame: End of study (up to week 187))

	Pediatric patients
Arm/Group Description	Pediatric patients (< 18

	years) treated with alpelisib
Number of Participants Analyzed [units: participants]	35
Notable vital sign values during the study period - Pediatric Patients (units: Participants) Count of Participants (Not Applicable)	
High Systolic blood pressure	17 (48.57%)
Low Systolic blood pressure	3 (8.57%)
High Diastolic blood pressure	12 (34.29%)
Low Diastolic blood pressure	2 (5.71%)
High Pulse rate	15 (44.12%)
Low Pulse rate	10 (29.41%)
High Weight	0 (%)
Low Weight	1 (3.45%)

Notable vital sign values during the study period - Adult Patients

(Time Frame: End of study (up to week 187))

	Pediatric patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18	Adult patients (>= 18 years)

	years) treated with alpelisib	treated with alpelisib
Number of Participants Analyzed [units: participants]	35	17
Notable vital sign values during the study period - Adult Patients (units: Participants) Count of Participants (Not Applicable)		
High Systolic blood pressure	17 (48.57%)	0 (%)
Low Systolic blood pressure	3 (8.57%)	0 (%)
High Diastolic blood pressure	12 (34.29%)	2 (11.76%)
Low Diastolic blood pressure	2 (5.71%)	0 (%)
High Pulse rate	15 (44.12%)	1 (5.88%)
Low Pulse rate	10 (29.41%)	0 (%)
High Weight	0 (%)	0 (%)
Low Weight	1 (3.45%)	6 (40%)

Number of participants with notable ECG values.

(Time Frame: Up to week 187)

	Pediatric Patients	Adult Patients
Arm/Group Description	Pediatric patients (< 18 years) treated	Adult patients (>= 18 years) treated with

	with alpelisib reporting ECG values	alpelisib reporting ECG values
Number of Participants Analyzed [units: participants]	3	3
Number of participants with notable ECG values. (units: Participants) Count of Participants (Not Applicable)		
QTcF New >450 to <=480 ms	1 (33.33%)	1 (50%)
QT Increase >30 to <=60 ms	1 (33.33%)	0 (%)
QT New >480 to <=500 ms	0 (%)	1 (33.33%)

Growth and development in pediatric population

(Time Frame: Week 24 or 6 months (± 4 weeks))

	pediatric patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	29
Growth and development in pediatric population (units: SD-score) Mean ± Standard Deviation	
Height SDS	-0.1 ± 1.23
Height velocity SDS	0.1 ± 5.01

BMI SDS	0.8 ± 1.21
Weight velocity SDS	-0.2 ± 2.86

Overview of number of patients with Adverse Events (AEs)

(Time Frame: Up to 187 weeks)

	Pediatric patients	Adult patients
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Number of Participants Analyzed [units: participants]	39	18
Overview of number of patients with Adverse Events (AEs) (units: Participants) Count of Participants (Not Applicable)		
Adverse events - All grades	31 (79.49%)	16 (88.89%)
Adverse events - Grade ≥ 3	4 (10.26%)	9 (50%)
SAEs - All grades	10 (25.64%)	11 (61.11%)
SAEs - Grade ≥ 3	3 (7.69%)	9 (50%)
AEs leading to dose reduction - All grades	0 (%)	3 (16.67%)
AEs leading to dose reduction - Grade ≥ 3	0 (%)	0 (%)
AEs leading to dose interruption - All grades	2 (5.13%)	3 (16.67%)

AEs leading to dose interruption - Grade ≥ 3	0 (%)	2 (11.11%)
AEs leading to treatment discontinuation	0 (%)	0 (%)
SAEs treatment-related - All grades	0 (%)	3 (16.67%)
SAEs treatment-related - Grade ≥ 3	0 (%)	1 (5.56%)

Safety Results

All-Cause Mortality

	Pediatric patients N = 39	Adult patients N = 18
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment or cut-off date whichever occurs first, up to maximum duration of 187 weeks

Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment or cut-off date whichever occurs first
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment

	Pediatric patients N = 39	**Adult patients N = 18**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Total participants affected	10 (25.64%)	11 (61.11%)
Blood and lymphatic system disorders		
Disseminated intravascular coagulation	0 (0.00%)	1 (5.56%)
Congenital, familial and genetic disorders		
Vascular malformation	2 (5.13%)	0 (0.00%)
Endocrine disorders		
Adrenal insufficiency	1 (2.56%)	0 (0.00%)
Gastrointestinal disorders		
Volvulus	0 (0.00%)	1 (5.56%)
Vomiting	1 (2.56%)	0 (0.00%)

General disorders and administration site conditions		
Fatigue	1 (2.56%)	0 (0.00%)
Gait disturbance	2 (5.13%)	0 (0.00%)
Impaired healing	0 (0.00%)	1 (5.56%)
Inflammation	0 (0.00%)	1 (5.56%)
Infections and infestations		
Cellulitis	1 (2.56%)	1 (5.56%)
Influenza	1 (2.56%)	0 (0.00%)
Otitis media acute	1 (2.56%)	0 (0.00%)
Streptococcal sepsis	0 (0.00%)	1 (5.56%)
Urinary tract infection	1 (2.56%)	0 (0.00%)
Injury, poisoning and procedural complications		
Fall	0 (0.00%)	1 (5.56%)
Multiple fractures	0 (0.00%)	1 (5.56%)
Post procedural discomfort	1 (2.56%)	0 (0.00%)
Pulmonary contusion	0 (0.00%)	1 (5.56%)
Metabolism and nutrition disorders		
Acidosis	1 (2.56%)	0 (0.00%)
Dehydration	1 (2.56%)	1 (5.56%)
Hyperglycaemia	0 (0.00%)	1 (5.56%)

Musculoskeletal and connective tissue disorders		
Back pain	0 (0.00%)	1 (5.56%)
Haematoma muscle	0 (0.00%)	1 (5.56%)
Pain in extremity	0 (0.00%)	2 (11.11%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Lipoma	1 (2.56%)	0 (0.00%)
Nervous system disorders		
Hypotonia	1 (2.56%)	0 (0.00%)
Lethargy	1 (2.56%)	0 (0.00%)
Renal and urinary disorders		
Renal impairment	0 (0.00%)	1 (5.56%)
Reproductive system and breast disorders		
Vaginal haemorrhage	0 (0.00%)	1 (5.56%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	1 (2.56%)	0 (0.00%)
Pneumomediastinum	0 (0.00%)	1 (5.56%)
Pulmonary embolism	0 (0.00%)	1 (5.56%)
Vascular disorders		
Thrombophlebitis	0 (0.00%)	1 (5.56%)

Venous thrombosis limb	0 (0.00%)	1 (5.56%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment or cut-off date whichever occurs first, up to maximum duration of 187 weeks
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment or cut-off date whichever occurs first
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Pediatric patients N = 39	**Adult patients N = 18**
Arm/Group Description	Pediatric patients (< 18 years) treated with alpelisib	Adult patients (>= 18 years) treated with alpelisib
Total participants affected	23 (58.97%)	16 (88.89%)
Blood and lymphatic system disorders		
Anaemia	0 (0.00%)	1 (5.56%)
Coagulopathy	0 (0.00%)	1 (5.56%)
Disseminated intravascular coagulation	2 (5.13%)	2 (11.11%)
Lymphopenia	1 (2.56%)	1 (5.56%)

Congenital, familial and genetic disorders		
Vascular malformation	2 (5.13%)	0 (0.00%)
Endocrine disorders		
Hyperparathyroidism	0 (0.00%)	1 (5.56%)
Hypothyroidism	0 (0.00%)	1 (5.56%)
Gastrointestinal disorders		
Abdominal pain	0 (0.00%)	1 (5.56%)
Anal fissure	0 (0.00%)	1 (5.56%)
Aphthous ulcer	3 (7.69%)	3 (16.67%)
Constipation	0 (0.00%)	1 (5.56%)
Diarrhoea	5 (12.82%)	4 (22.22%)
Haemorrhoids	0 (0.00%)	2 (11.11%)
Nausea	1 (2.56%)	1 (5.56%)
Rectal haemorrhage	0 (0.00%)	1 (5.56%)
Stomatitis	3 (7.69%)	0 (0.00%)
Toothache	1 (2.56%)	1 (5.56%)
Vomiting	0 (0.00%)	1 (5.56%)
General disorders and administration site conditions		
Asthenia	0 (0.00%)	1 (5.56%)
Gait disturbance	0 (0.00%)	1 (5.56%)
Inflammation	3 (7.69%)	1 (5.56%)
Infections and infestations		

Abscess soft tissue	0 (0.00%)	1 (5.56%)
Bronchitis	0 (0.00%)	1 (5.56%)
Cellulitis	0 (0.00%)	1 (5.56%)
Cystitis	0 (0.00%)	1 (5.56%)
Erysipelas	0 (0.00%)	1 (5.56%)
Nasopharyngitis	0 (0.00%)	1 (5.56%)
Prostatitis Escherichia coli	0 (0.00%)	1 (5.56%)
Soft tissue infection	0 (0.00%)	1 (5.56%)
Urinary tract infection	0 (0.00%)	1 (5.56%)
Viral infection	2 (5.13%)	0 (0.00%)
Investigations		
Weight decreased	1 (2.56%)	1 (5.56%)
Metabolism and nutrition disorders		
Decreased appetite	0 (0.00%)	1 (5.56%)
Folate deficiency	0 (0.00%)	1 (5.56%)
Hyperglycaemia	2 (5.13%)	4 (22.22%)
Hypoglycaemia	3 (7.69%)	0 (0.00%)
Type 2 diabetes mellitus	0 (0.00%)	1 (5.56%)
Musculoskeletal and connective tissue disorders		
Back pain	0 (0.00%)	1 (5.56%)
Osteoarthritis	0 (0.00%)	1 (5.56%)
Pain in extremity	1 (2.56%)	1 (5.56%)
Scoliosis	0 (0.00%)	1 (5.56%)

Nervous system disorders		
Dizziness	1 (2.56%)	1 (5.56%)
Headache	0 (0.00%)	3 (16.67%)
Memory impairment	0 (0.00%)	2 (11.11%)
Sciatica	1 (2.56%)	1 (5.56%)
Somnolence	0 (0.00%)	1 (5.56%)
Psychiatric disorders		
Libido decreased	0 (0.00%)	1 (5.56%)
Reproductive system and breast disorders		
Erectile dysfunction	0 (0.00%)	1 (5.56%)
Haematospermia	0 (0.00%)	1 (5.56%)
Menstruation irregular	0 (0.00%)	1 (5.56%)
Prostatitis	0 (0.00%)	1 (5.56%)
Vaginal ulceration	0 (0.00%)	1 (5.56%)
Vulvovaginal dryness	0 (0.00%)	1 (5.56%)
Vulvovaginal pain	0 (0.00%)	1 (5.56%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	1 (2.56%)	1 (5.56%)
Sleep apnoea syndrome	1 (2.56%)	1 (5.56%)
Skin and subcutaneous tissue disorders		
Acne	0 (0.00%)	1 (5.56%)
Alopecia	0 (0.00%)	3 (16.67%)

Angioedema	0 (0.00%)	1 (5.56%)
Dry skin	1 (2.56%)	3 (16.67%)
Eczema	1 (2.56%)	3 (16.67%)
Skin ulcer	0 (0.00%)	2 (11.11%)
Vascular disorders		
Haematoma	0 (0.00%)	1 (5.56%)
Hot flush	0 (0.00%)	1 (5.56%)
Thrombophlebitis superficial	0 (0.00%)	1 (5.56%)
Thrombosis	0 (0.00%)	1 (5.56%)
Varicose vein	0 (0.00%)	1 (5.56%)

Other Relevant Findings

None

Conclusion:

- Results from this study demonstrates that targeting the underlying cause of the PROS disease (PIK3CA gene mutation) is a valid treatment approach offering a meaningful clinical benefit to patients. The patient population that was included in this study had a confirmed mutation in the PIK3CA gene and appropriately represents a broader group of patients in terms of age, gender, and disease characteristics. Therefore, it is expected that the overall population with PROS may derive clinical benefit from treatment with alpelisib.

- Treatment with alpelisib is associated with shrinkage of PROS lesions by at least 20% at Week 24 (37.5%) and without progression of the disease or requiring rescue surgery.
  Additionally, 74.2% of the patients with a radiological assessment available at Week 24 had a decrease in the volume of the selected target lesions.
- Majority of the patients treated with alpelisib in this study derived clinical benefit, confirmed by the sustained improvement in PROS-related signs, symptoms and complications across the Full study population.
- Furthermore, no new safety concerns have been identified either in pediatric or adult patients, and the safety profile observed was consistent with the current knowledge of the product safety profile, comparing favorably with experience in the adult patients with advanced breast cancer. Notably, the low frequency and mild severity of AEs suggest acceptable tolerability and a manageable safety profile consistent with the known mechanism of action of the drug.

Date of Clinical Trial Report

23-Aug-2021