EPIK-P2: A Phase II double-blind study with an upfront, 16-week randomized, placebo-controlled period, to assess the efficacy, safety and pharmacokinetics of alpelisib (BYL719) in pediatric and adult patients with PIK3CA-related overgrowth spectrum (PROS)

Published: 14-01-2021
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-508530-34-00 check the CTIS register for the current data. Primary objective:* To demonstrate the efficacy of alpelisib as measured by the proportion of participants randomized to alpelisib with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON54117

Source
ToetsingOnline

Brief title
CBYL719F12201 (EPIK-P2)

Condition

- Miscellaneous and site unspecified neoplasms benign
- Skin vascular abnormalities
- Skin and subcutaneous tissue therapeutic procedures

Synonym
PIK3CA-related overgrowth

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor van dit onderzoek)

Intervention

Keyword: alpelisib, overgrowth spectrum (PROS), Phase II, Phase II., PIK3CA-related

Outcome measures

Primary outcome

Endpoint for primary objective:

Response (yes/no) defined by achieving at least 20% reduction from baseline in

the sum of target lesion volumes (1 to 3 lesions, assessed by MRI by a blinded

independent review committee (BIRC)) at Week 24, provided that none of the

individual target lesions has >= 20% increase from baseline

and in absence of progression of non-target lesions and without new lesions.

Confirmation of response requires a subsequent imaging assessment performed at

least 4 weeks after the onset of the response.See Section 2.1 for Primary

Estimands and Section 8.3 for response definition.

Secondary outcome

Endpoint for key secondary objective:

Response at week 16 (by BIRC): See Section 2.2 for secondary Estimands and

Section 8.3 for response definition.

To assess the efficacy of alpelisib as measured by the proportion of

participants with a response at Week 24 (by BIRC) in Groups 1 and 2

For endpoints for other and exploratory objectives see also protocol section 2

(Objectives, endpoints and estimands

Study description

Background summary

The results described in preclinical studies including a mouse model have shown that alpelisib inhibits the PI3K/AKT/mTOR signaling pathway and rescues the PROS phenotype in the mouse model efficaciously. The first reported case series demonstrated that alpelisib is clinically effective and well tolerated by both pediatric and adult participants with PROS. The drug improved the disease symptoms in all 19 participants treated in a single center over a variable period of time (beyond 18 months for some participants) (Venot et al 2018). Alpelisib demonstrated therapeutic activity in participants with PROS regardless of the type of PIK3CA mutation and was effective in treatment naive participants and those who previously received mTOR inhibitor Sirolimus. The first experience with alpelisib in overgrowth related to mutation in PIK3CA gene provides the direct evidence of clinical improvement in participants supporting PIK3CA inhibition as a promising therapeutic strategy in participants with PROS.

In Aug-2021, results from EPIK-P1 (CBYL719F12002) study, a retrospective noninterventional study of 57 patients with PIK3CA Related Overgrowth Spectrum (PROS) were available and later presented at the European Society for Medical Oncology (ESMO) congress 2021 (Canaud et al 2021). This study*s results provide evidence of meaningful clinical benefit of alpelisib for the treatment of patients aged 2 years and older with PROS.

The EPIK-P1 data supports the first direct evidence of clinical improvement in PROS participants reported by Venot et al (2018) and confirms that PIK3CA inhibition is a promising therapeutic strategy in participants with PROS.

See also protocol section 1.1 (background)

Study objective

This study has been transitioned to CTIS with ID 2023-508530-34-00 check the CTIS register for the current data.

Primary objective:
* To demonstrate the efficacy of alpelisib as measured by the proportion of participants randomized to alpelisib with a response at Week 24 in at least one of the following groups:
* Group 1 (>= 18 yr-old)
* Group 2 (6 - 17 yr-old)

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

For other secondary objectives and exploratory objectives see also protocol section 2 (Objectives, endpoints and estimands)

Study design

The study is a Phase II multi-center study with an upfront 16-week, randomized, double-blind, placebo-controlled period, and extension periods, to assess the efficacy, safety and PK of alpelisib in pediatric and adult participants with PROS.

A total of approximately 156 participants (of age >= 6 years) will be randomized in the study. Two additional groups of approximately 12 participants in Group 3 (2 to 5 years old) and 6 participants in Group 4 (2 to 5 years old) will be enrolled for exploratory purposes.

Core, Extension 1 and Extension 2 periods will be applied to the participants >=6 years old (Group 1 - adults, Group 2 - participants 6 to 17 years old). Group 3 will include the participants who are 2 to 5 years old and it will be an exploratory group.
Group 1 and Group 2 will be enrolled in parallel. Group 3 will be enrolled later, after 24-week efficacy, safety and PK data are available from the first two age groups, in order to select the recommended dose for this group.

Group 4 will be open to enrollment immediately after the implementation of Global Protocol Amendment 01, whereas Group 3 will be open to enrollment after the primary analysis of patients in Groups 1 and Group 2 will be available and only after implementation of a future substantial Global Protocol Amendment

Group 5 of approximately 15 participants, 6 to 17 years of age, will be open to enrollment immediately after the implementation of Global Protocol Amendment 02.

See also protocol section 3 (Study design)

Intervention

Groups 1 and 2: Intervention with alpelisib or placebo in the first 16 weeks. From week 17 onwards alpelisib.

The participants in Group 4 will receive alpelisib FCT 50 mg once daily in an open-label setting

Group 3 will be enrolled later, when the 24-week efficacy, safety and PK data are available from the other participants, in order to select the appropriate dose for this group. The participants in Group 3 will receive alpelisib in an open-label setting, Group 3 will be an exploratory group.

Group 5 of approximately 15 participants, 6 to 17 years of age, treated with a starting dose of 125 mg alpelisib film-coated tablets.

For more details, please refer to Section 3 Study Design.
Details are presented in Table 6-1, Table 6-2, Table 6-3, Table 6-4 , Table 6-5.

Study burden and risks

Risk: potential side effects of study treatment

Burden:
A tumor sample will be taken for PIK3CA mutation testing in case no tissue is available.

The patient will come to the study doctor*s clinic 8 times in the first 24 weeks; 6 times in the second 24 weeks (till week 48) and then every 24 weeks till end of study (week 264). After the patient discontinues study treatment, he/she will be followed for safety.

See question E4 for all study assessments.

Contacts

Public
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL
Scientific

Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients with diagnosis of PROS with symptomatic and /or progressive overgrowth and at least one measurable PROS-related lesion confirmed by blinded independent review committee (BIRC) assessment
2. Documented evidence of a somatic mutation(s) in the PIK3CA gene performed in local laboratories
3. A tissue sample (fresh or archival) must be available to be sent to a Novartis-designated central laboratory. If archival tissue is not available, collection of a fresh tissue biopsy is required for participants in Groups 1, 2 and 5, if it is not clinically contraindicated. For participants in Groups 3 and 4, a fresh tissue biopsy is not mandatory.
4. Karnofsky (in patients > 16 years old at study entry)/Lansky (<=16 yrs of age at study entry) performance status index >=50
5. Adequate bone marrow and organ function including Fasting plasma glucose (FPG) <= 140 mg/dL (7.7 mmol/L)* and Glycosylated hemoglobin (HbA1c) <= 6.5% (both criteria have to be met) (as assessed by central laboratory for eligibility within.
6. Presence of at least one PROS-related measurable lesion defined as a lesion with longest diameter >=2 cm, when the volume can be accurately and reproducibly measured by MRI, and associated with complaints, clinical symptoms or

functional limitations affecting the patient's everyday life. Measurability must be confirmed by BIRC before randomization.

For the full inclusion criteria, please refer to Section 5.1. of protocol

Exclusion criteria

1. Participant with only isolated macrodactyly, epidermal nevus/nevi and macroencephaly (the only clinical feature or a combination of any of three of them), in absence of other PROS-related lesions at the time of informed consent.
2. Previous treatment with alpelisib and/or any other PI3K inhibitor(s) (except treatment attempt, defined as the attempt to treat PROS with any of PI3K inhibitors, with treatment duration less than 2 weeks and stopped at least 4 weeks prior to the first dose of study medication with alpelisib)
3. Radiation exposure for PROS treatment purpose within the previous 12 months on those PROS areas which are expected to qualify for target lesions (except lesion(s) progressing after completion of radiotherapy) at time of informed consent.
4. Debulking or other major surgery performed within 3 months at time of informed consent.
5. Clinically meaningful PROS-related thrombotic event (Grade 2 and more as per CTCAE v.4.03) within 30 days before informed consent, and/or sclerotherapy/embolization for vascular complications performed within 6 weeks before informed consent. Participants (receiving anticoagulants for PROS-related coagulopathy, primary or secondary prophylaxis of thrombosis may be included in the study).
6. Participants with documented pneumonitis or interstitial lung disease at time of informed consent.
7. History of acute pancreatitis within 1 year before informed consent or past medical history of chronic pancreatitis at time of informed consent.
8. Participants with an established diagnosis of type I diabetes mellitus or uncontrolled type II diabetes mellitus at time of informed consent.
9. Known history of seizure, or epilepsy, regardless of relatedness to PROS sprectrum at time of informed consent, when epilepsy is not controlled and/or the patient may not be switched to non-enzyme inducing antiepilectic drug(s) at time of informed consent.
10. Participants with clinically significant worsening of the PROS-related signs and symptoms (e.g. increase of D-dimers, worsening of underlying pain, newly occurring swelling or redness) indicating an uncontrolled condition during screening phase, particularly if systemic treatment with any other inhibitor of the PI3K/AKT/mTOR pathway was stopped prior to the start of the study treatment. This includes but is not limited to hypercoagulability state in participants not receiving prophylactic treatment.

For the full inclusion criteria, please refer to Section 5.2 of protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-01-2022
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Piqray
Generic name:	alpelisib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-01-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	19-04-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	26-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	11-03-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-508530-34-00
EudraCT	EUCTR2020-000561-16-NL
ClinicalTrials.gov	NCT04589650
CCMO	NL74406.091.20