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A phase II double-blind multicentre, placebo-controlled trial to assess the efficacy and safety of alpelisib (BYL719) in paediatric and adult patients with Megalencephaly-CApillary malformation Polymicrogyria syndrome (MCAP): the SESAM study protocol

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ABSTRACT

Introduction The megalencephaly capillary malformation polymicrogyria (MCAP syndrome) results from mosaic gain-of-function *PIK3CA* variants. The main clinical features are macrocephaly, somatic overgrowth, neurodevelopmental delay and brain anomalies. Alpelisib (Vijoice) is a recently FDA-approved PI3Kα-specific inhibitor for patients with PIK3CA-related overgrowth spectrum (PROS). During its development, in patients with the MCAP subgroup of PROS, there was no specific, standardised evaluation of the effect on neuro-cognitive functioning. Moreover, it remains unknown if the molecule crosses the blood-brain barrier. Our objective is to evaluate the efficacy of a 24 month treatment with alpelisib on adaptive behaviour in patients with MCAP syndrome.

Methods and analysis SESAM is an industry-sponsored two-period multicentre French academic phase II trial, with a 6-month double-blind, placebo-controlled period followed by an open-label period. The primary endpoint is a ≥4-point improvement in the Vineland II Adaptive Behaviour Scale (VABS), 24 months after treatment initiation. Secondary objectives are safety, VABS improvement at 6 months, impact on the quality of life, epilepsy and hypotonia. 20 patients aged 2 to 40 years with an MCAP diagnosis and neurodevelopmental disorders of various degrees, will be followed monthly in local centres, centrally assessed (clinical, biological, neuropsychological and functional evaluation) at baseline and every 6 months. Patients will be evaluated by volumetric MRI at baseline and at 24 months. An optional lumbar puncture will be performed to investigate blood-brain barrier crossing. Inclusions were completed by April 2024, with the end of follow-up in November 2026.

Given the efficacy of alpelisib in patients with PROS, if the drug crosses the blood-brain barrier, we can expect a clinical benefit for patients with neurocognitive disorders.

Ethics and dissemination Ethical approval was given by CPP Sud-Ouest et Outre-Mer I (reference: 2022-500197-34-01). Findings from this study will be disseminated via publication, reports and conference presentations.

Trial registration number NCT05577754

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The SESAM trial is the first evaluation of alpelisib dedicated to patients with megalencephaly capillary malformation polymicrogyria using neurocognitive endpoints.
⇒ The passage of alpelisib through the blood-brain barrier will be evaluated in the SESAM trial.
⇒ The two-period design (double-blind placebo-controlled period followed by the open-label period) has been chosen to comply with the best-quality methodological standards.
⇒ Heterogeneity in a patient's clinical presentation represents a challenge in the interpretation of the results.
⇒ No international consensus exists on the scales to be used in clinical trials in patients with neurocognitive disorders.

INTRODUCTION

Segmental overgrowth disorders (SODs) are rare conditions usually characterised by abnormal and asall cells and not symetric

growth of some parts of the body. This excessive tissue growth is caused by an overactivation of the cell proliferation mechanism. Mosaic-activating variants in the p110α catalytic subunit of phosphatidylinositol-3 kinase (PI3K; encoded by the *PIK3CA* gene) have been identified in a subset of SODs. The PI3K-AKT-mTOR is a critical signalling pathway in regulating proliferation, survival and cell growth. Activating variants in *PIK3CA* lead to increased PI3K-AKT-mTORC1 axis activation, which in turn promotes excessive growth in affected tissues.[1–6]

The PIK3CA-related overgrowth spectrum (PROS) is a congenital condition with progressively asymmetric overgrowth, which can begin in the antenatal period. This disease is wide-ranging and depends on the timing of the founder mutation in embryogenesis.[6–9] Depending on the clinical presentation (segmental body overgrowth or brain disorder), three main disease subgroups can be distinguished: the CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal/spinal anomalies), the Klippel–Trenaunay syndrome and the megalencephaly capillary malformation polymicrogyria (MCAP) syndrome. CLOVES clinical presentation ranges from isolated digit enlargement to extensive overgrowth of the limbs, thorax/abdomen and/or face. It may be accompanied by vascular or lymphatic malformations, epidermal nevi and spinal anomalies. Associated morbidity can be highly variable, but can include functional impairment, debilitating haemorrhages and thromboses, and, in some cases, can be lethal. For patients with Klippel–Trenaunay syndrome, vascular malformations are often in the foreground, associated with soft tissue and bone hypertrophy, and involve one limb, most often the lower limb. MCAP is characterised by megalencephaly (large head), capillary malformation of the skin (middle face, limbs and trunk), abnormalities of the extremities and possible abnormalities of the brain structure (Chiari malformation, hydrocephalus, polymicrogyria).[9 10] Megalencephaly is present at birth, and the brain continues to develop gradually during the first postnatal years with a relative stabilisation with age, although remaining larger than normal. MCAP patients may experience impaired cognition, hypotonia, variable intellectual deficiency and seizures. Abnormalities of the brain structure may be present (hydrocephalus, Chiari malformation and polymicrogyria in particular). Asymmetry of some body parts may also exist, as well as skin manifestations. Cardiac and genitourinary abnormalities have been reported in rare cases. The current diagnosis is established through a clinical evaluation and genetic testing on the affected tissues. In rare cases, the *PIK3CA* variant is present in all cells and not in a mosaic state. MRI is used to identify and monitor brain abnormalities. The French National Protocol for Diagnosis and Care for MCAP syndrome[11] and an international expert consensus statement for standardising care for individuals with *PIK3CA*-related disorders have been published.[12] As patients may be misdiagnosed, the true disease prevalence is not well known. But in France, in 2021, more than 60in oncology in MCAP patients had already been genotyped. Variability in the degree of neurocognitive manifestations is considerable, ranging from mild learning disabilities to profound intellectual disability, in some cases associated with epilepsy.[10]

The natural history of PROS shows that most of the overgrowth progression occurs during early childhood, emphasising the need to assess the potential benefit of early treatment in paediatric patients with PROS. It could avert associated complications and/or surgery by decreasing disease progression at this active stage.

Interestingly, drug treatments that specifically inhibit the p110α catalytic subunit of PI3K have been developed in oncology in the case of tumours with *PIK3CA* gain-of-function variants. Alpelisib (Vijoice, Novartis Pharmaceutical) has been authorised in metastatic breast cancer[13 14] and has therefore been investigated through drug repurposing in PROS, in a case series of 19 French patients under a compassionate approach, including two with MCAP.[15] After encouraging results in safety and efficacy, Novartis Pharmaceutical started the EPIK programme. The EPIK-P1 (NCT04285723) is a real-world study for demonstrating clinical benefits in people with PROS, and EPIK-P3 (NCT04980833) is a phase II study to assess the long-term safety and efficacy of alpelisib in people with PROS who participated in EPIK-P1. The ongoing international prospective phase II double-blind, randomised, placebo-controlled study clinical trial (EPIK-P2, NCT04589650) is assessing the efficacy, safety and pharmacokinetics of alpelisib in paediatric and adult patients with PROS. Positive preliminary results from EPIK-P1 led the FDA to grant early April 2022, an accelerated approval for alpelisib (Vijoice) in PROS, including MCAP, for patients of 2 years of age and over, based on the efficacy (defined as a ≥20% reduction from baseline in the sum of measurable target lesion volume) observed in 37 patients from EPIK-P1 after 6 months of treatment.[16] However, these therapeutic studies preferentially targeted patients with CLOVES or Klippel–Trenaunay syndromes, and endpoints were not designed to assess neurocognitive improvement. Current data on alpelisib efficacy and safety in MCAP patients solely come from compassionate use, which fails to demonstrate a clear benefit of the treatment on neurocognitive symptoms.[15 17] There is even no proof that alpelisib crosses the blood-brain barrier.

To assess the clinical benefit of Alpelisb in MCAP patients, it was necessary to construct a clinical trial evaluating specifically neurocognitive functions. Based on the clinical and radiological evaluation of 33 French patients with MCAP syndrome,[10] we designed

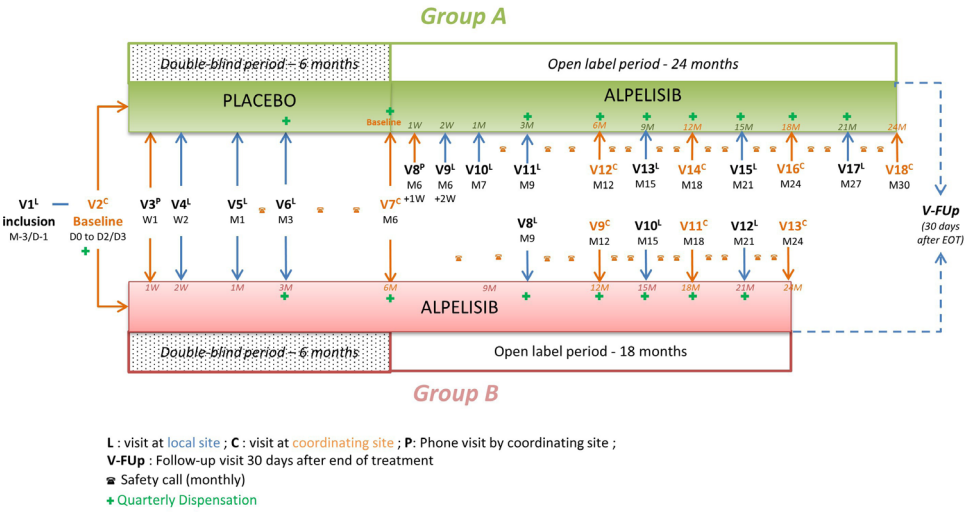

Figure 1 Study design of the SESAM trial.

the SESAM study to assess the safety and efficacy of alpelisib in these patients and its passage across the blood-brain barrier.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This study is promoted, partly funded and coordinated by Dijon Bourgogne University Hospital. Drug supply and part of the funding was supported by Novartis Pharmaceutical. It includes paediatric and adult patients covered by national health insurance. To minimise the logistic burden for the patients, inclusion and safety visits are performed in their local hospitals (nine sites in total). Two evaluating sites (Dijon Bourgogne University Hospital and Paris Necker Hospital) are in charge of the baseline and assessment visits.

Study design, participant, randomisation

Study design

The SESAM trial is a two-period multicentre phase II trial, with 6 months double-blind, placebo-controlled period followed by an open-label period (figure 1). Patients and their legal representatives are given by the investigator a consent form adapted to their age and ID severity (see online supplemental material for the detailed consent forms). A separate and optional consent for lumbar puncture is also proposed. After validation of the screening exams at the inclusion visit, patients are randomised to take alpelisib (250 mg/day for adults or 50 mg/day for children) or a placebo for 6 months with a 1:1 ratio. A first evaluation will be performed at 6 months (secondary objective 1) to determine the response status, and patients will be unblinded once the evaluation is done. Patients completing the double-blind phase will then be entered into an open-label phase as follows: patients on placebo will switch to alpelisib (250 mg/day for adults or 50 mg/day for children), responders to alpelisib will continue alpelisib at the same dose during 18 months, and non-responders will have their dose increased (300 mg/day for adults, 125 mg/day for children ≥6 years old only). The dose increase is not permitted for children aged 5 years and below. Non-responders are patients who did not experience sufficient clinical benefit (based on overall clinical response assessed by the investigator) and with no safety/tolerability concerns, which may preclude from treatment continuation at a higher dose level. Patients will undergo additional evaluation visits every 6 months and a final evaluation visit after 24 months of alpelisib treatment (main objective). Patients will undergo a main evaluation visit with clinical, biological, functional and neurocognitive exams every 6 months. Safety monitoring will be assured on a monthly basis. The schedule and content of the visits are detailed in the online supplemental material (Annex 1 a and 1b).

Participants

Patients aged 2–40 years, with documented evidence of postzygotic or constitutional variant(s) in *PIK3CA* and a diagnosis of MCAP with a neurocognitive disorder (from specific learning disorder to severe intellectual disability) at the time of consent could be included. The main exclusion criteria are related to contraindications to alpelisib treatment such as history of pancreatitis, diabetes or pneumonitis. The exhaustive list of inclusion and exclusion criteria is detailed in annex 2 of online supplemental material 2.

Randomisation

Randomisation will be performed by the site staff using the centralised tool in the e-CRF at baseline visit, only after confirming that the participant fulfils all the inclusion/exclusion criteria. The investigator will have to confirm the key eligibility criteria checklist embedded in

the system to access to randomisation tool in the e-CRF. A statistician from Dijon Bourgogne University Hospital, independent of the research, will edit the randomisation list, prior to the start of the trial. Breaking of blinding can be requested by the investigator for the occurrence of serious adverse events requiring knowledge of the experimental product to determine the therapeutic course to be taken, by the unblinding function in the randomisation tool in the e-CRF.

Objectives

Primary objective

The primary objective is to assess the efficacy on adaptive behaviour after 24 months of alpelisib treatment.

Secondary objectives

To assess (1) the efficacy of alpelisib vs placebo on adaptive behaviour based on the comparison of the proportion of participants with response at 6 months in each group, (2) the impact of alpelisib treatment on cerebral and spinal cord vascularisation and volume and (3) the safety of alpelisib treatment.

Exploratory objectives

To evaluate the effects of alpelisib on (1) the early efficacy of alpelisib on adaptive behaviour, (2) quality of life and clinical global impression, (3) neuropsychological parameters, (4) epilepsy, (5) overgrowth and skin lesions when appropriate, (6) hypotonia and (7) to quantify alpelisib passage throughout the blood-brain barrier and its relationship with systemic exposure of alpelisib.

Study endpoints

Primary outcome

According to the publication by Chatham *et al*,[18] clinically meaningful improvement will be defined as a gain of at least four points in the Vineland II Adaptive Behaviour Scale (VABS-II) at 24 months of treatment compared with baseline. The VABS-II is the most widely used scale to assess day-to-day adaptive skills, from birth to adulthood.[19 20] It consists of a form which will be filled during an interview with an adult who is familiar with the activities of daily living of the patients (usually a parent). The VABS-II is organised within a three-domain structure: communication, daily living skills, and socialisation. In addition, VABS-II has a motor skills domain for children younger than 6 years of age, and an optional maladaptive behaviour index.[19 20] The domain (communication, daily living skills, and socialisation) standard scores have a mean of 100 and a SD of 15. Adaptive levels can also be determined. A global standard score can also be computed (the Adaptive Behaviour Composite standard score) and also has a mean of 100 and a SD of 15.

Secondary outcomes

For the secondary objectives, the corresponding outcomes will include:

1. The response (yes/no) defined as an improvement of at least four points in the VABS-II at 6 months of treatment in the alpelisib group compared with the placebo group.
2. The changes in brain volume, vascularisation, structural connectivity, assessed by MRI, from baseline to the end of the treatment period.
3. The number, type and severity of adverse events.

Exploratory outcomes

Exploratory endpoints will assess the following:

1. Improvement of at least four points in the VABS-II at 6, 12 and 18 months of treatment, compared with baseline.
2. Evolution of quality-of-life questionnaires, scores at the visual analogue scale and evolution of Clinical Global Impression of severity and Global improvement scores at 6, 12, 18 and 24 months of treatment, compared with baseline.
3. Changes in neuropsychological scales, adapted to age, at 12 and 24 months of treatment compared with baseline for attention, cognition, visuo-spatial disorders, fine motor skills, speech, reasoning and cognitive inhibition abilities, and at 24 months of treatment compared with baseline for the IQ scale.
4. Description of changes in seizure frequency (weekly diary), and antiepileptic drug use at 6, 12, 18 and 24 months of treatment compared with baseline.
5. Changes in overgrowth or skin lesions were classified as follows: increase, no changes or reduction in overgrowth or skin lesions according to clinical measures and evaluation of standardised photographs taken at 6, 12, 18 and 24 months of treatment compared with baseline.
6. Changes in Motor Function Measure (MFM) scores at 6, 12, 18 and 24 months of treatment compared with baseline.
7. Level of alpelisib (ng/mL) in the cerebrospinal fluid (CSF) and in the blood at between 6 or 24 months of treatment and the correlation estimate (rho) between CSF and blood levels of alpelisib.

The versions of each scale or questionnaire according to age are detailed in figure 2.

Sample size calculation

The assumptions are as follows: (1) when following untreated MCAP patients 6.0% at best may have experienced the four point improvement, (2) the minimal requirement for the treatment to be considered clinically relevant by regulatory bodies is at least one-third of the treated patients (33%) experiencing the four point improvement. With alpha=0.05, 1-beta=0.90 and a bilateral test, 16 patients are needed to prove the statistical difference between the theoretical and observed proportion. We are thus planning to enrol and analyse 20 patients to take account of possible loss of follow-up or withdrawal of consent. The approach for sample size calculation is also pragmatic based on known and estimated cohorts. A cohort of about 60 patients with MCAP and *PIK3CA* pathogenic variants

is available, two-thirds of them having ID or learning disability that could justify being enrolled in a clinical trial. If a patient is withdrawn from the study before treatment initiation, he will be replaced to be able to conduct the comparison between alpelisib and placebo groups with 10 patients in each group.

PATIENT AND PUBLIC INVOLVEMENT

The feasibility of recruitment is assured by the participation of experts in the clinical and molecular aspects of PROS, including the French reference centre for mosaic disorders, the RHU COSY[21] and the French patient association for MCAP (M-CM France).

DATA MANAGEMENT AND DATA ANALYSES

Data collection, monitoring and management

Clinical, biological and radiological data will be entered directly into a dedicated electronic Case Report Form (e-CRF) on the CleanWEB platform by the investigators, helped by the Clinical Research Associate (CRA). The patient diary is paper-based and will be reviewed by the investigator to capture the safety events that will be entered in the e-CRF. Each patient is identified by a unique code including the number of the recruiting centre, the inclusion rank and the initials of the patient (first letter of surname and first name). Automatic queries due to missing and incoherent data after data entry can be immediately generated by the CleanWEB software. Requests for corrections may also be generated by the methodological support unit of CHU Dijon and sent to the local and/or the evaluation centre. The corrections will be made directly in the e-CRF by the investigators, assisted by the CRAs. Histories of changes are systematically recorded. Additionally, a CRA will perform an on-site exhaustive data monitoring for all patients. A data management plan, specific to the study, was prepared before initiating the study in the participating centres.

Statistical analyses

Descriptive analysis

Descriptive analysis with the presentation of the baseline characteristics of the cohort, with qualitative variables expressed as the number of events with their frequencies (%), with their two-sided exact 95% CI. For quantitative variables, mean (±SD) or median (IQR) values will be calculated.

Primary outcome analysis

Fisher's exact test or χ square test will be used to compare the observed proportion of patients reaching the primary endpoint after 24 months of treatment to the theoretical proportion of 6%. A $p<0.05$ will be considered significant.

Secondary analyses

The same approach will be used to compare the proportion of responders at M6 between the alpelisib and placebo groups. Comparison of brain volumes (affected and unaffected zones) after 24 months of treatment vs baseline will be performed using a paired-t-test or Wilcoxon rank test according to the distribution priorly assessed by a Shapiro–Wilk test.

For all safety analyses, data recorded during monitoring for adverse events (AEs), either clinical or biological, will be collated and the number, type grade of AE, and their relation to treatment, will be described and the frequencies of AEs recorded as percentages and 95% CI. Results will be presented for the overall 24-month-period of treatment and also specifically for the double-blind period, to compare safety between alpelisib and placebo.

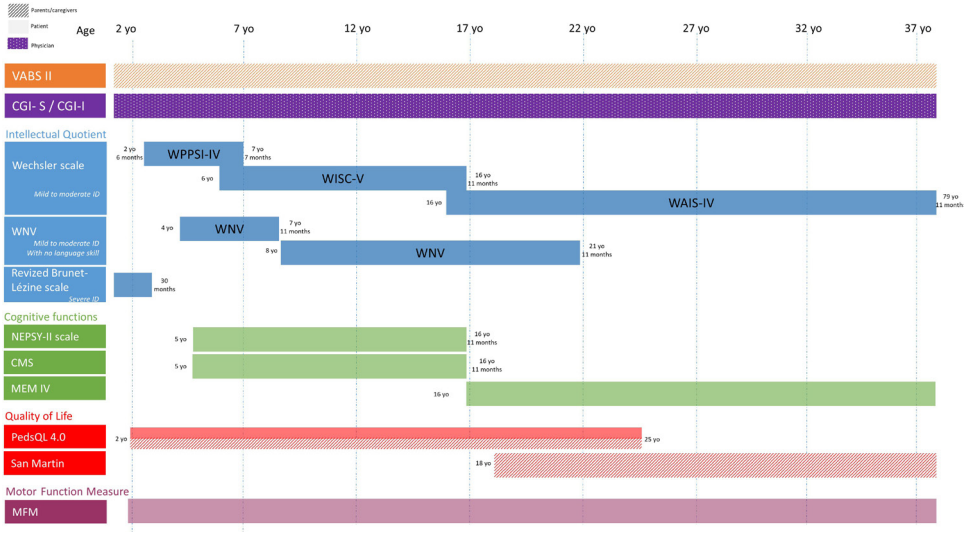

Figure 2 Neuropsychological tests used in the SESAM trials. Tests were selected according to the conclusions of a working group from the DéfiScience Network (www.defiscience.fr), which assessed all the neuropsychological tests available for each domain and adapted to ID patients. The 20-item Motor Function Measure (MFM20) will be administered for children <7 years old and the MFM32 for children ≥7 years old.

The CTCAE (v5.0) classification will be used to grade the events.

Exploratory analyses

Comparison of the mean scores of neuropsychological scale scores obtained at baseline and M24 will be performed using a paired-t-test or Wilcoxon rank test. To test the reliability of the change, the reliable change index (RCI) will be calculated for each psychometric scale.[22]

For fine reasoning and cognitive inhibition abilities, the raw data (logfiles from Presentation software) will be analysed automatically using Matlab 7.1. A reaction time (RT) and an error rate (ER) analysis will be performed using R software (see online supplemental material; Annex 3).

Changes in scores at the MFM test will be assessed by analysing the slopes of change between scores obtained at 6, 12, 18 and 24 months of treatment vs baseline for each patient and expressed as an annual rate using the unweighted least-square estimate. Comparison of the mean scores will then be performed using a paired-t-test or Wilcoxon rank test.

Finally, the correlation between the CSF level and blood level of alpelisib will be estimated by calculating the factor rho of Spearman's correlation.

Statistical software

Analysis will be performed using SAS software (version 9.4). Statisticians will be blinded to the study.

METHODS: MONITORING

Harms: steering data and safety monitoring committees

The coordinating centre at University Hospital Dijon-Bourgogne, Clinical Investigation Centre (CIC INSERM 1432), is assigned the responsibility of all study aspects: ethical, regulatory, study coordination, data management and publication strategy.

The steering committee is composed of the coordinating investigator, a methodologist, a pharmacovigilance officer, a pharmacist, a sponsor representative and the project manager. This committee meets on a weekly basis to assess study progress and solve potential issues.

An independent data safety monitoring board (DSMB) is monitoring the patients' safety during the study and gives recommendations to the steering committee. It is composed of a pharmacologist or pharmacovigilant officer, a methodologist, a neuropediatrician and a geneticist. The DSMB met when the first four included patients (25% of the initially anticipated number of patients) had completed 1 month of treatment and will meet again at 50% and 75% of the inclusions. Treatment initiations will be halted at each threshold and will resume after reviewing the safety data by the DSMB.

ETHICS AND DISSEMINATION

Authorisation was obtained from the French National Drug Safety Agency on 28 July 2022 and from the ethics committee (CPP Sud-Ouest et Outre-Mer I) on 22 September 2022 (reference number: 2022-500197-34-01). The protocol was registered with ClinicalTrials.gov under the identifier NCT05577754 on 13 October 2022. The current version of the protocol is V3 (25/05/2023). The first patient was included in November 2022, and the study is expected to be completed by April 2026.

Results will be presented at scientific meetings and published in international peer-reviewed journals.

DISCUSSION

At present, there is no licensed or unlicensed drug with a proven benefit for patients with MCAP syndrome, although alpelisib FDA's approval for patients with PROS, based on a collection of real-world evidence from compassionate use, makes it possible to treat patients with MCAP syndrome. As such, there is a clear unmet medical need. The understanding of the pathophysiology of the PROS and MCAP syndromes, a *PIK3CA* gain-of-function variant and the development of specific PI3K3 inhibitors in cancer, where the same variants are found, has raised great hopes of eventually providing an effective treatment.

Although Novartis Pharmaceutical's sponsored EPIK-P2 is running for patients with PROS, no such study was planned for patients with MCAP syndrome. Even if the data are sparse, Venot *et al* reported that the two patients with MCAP syndrome among the 19 patients with PROS syndrome exhibited improvement in cognitive function, behaviour and cerebral perfusion.[15] We, therefore, hypothesised that alpelisib treatment could be useful for these patients and designed a dedicated trial.

The judgement criteria for the SESAM study were based on the collection of complete clinical and radiological data from 33 French patients, which we published in 2021.[10] It was this cohort that led us, for example, not to adopt the evolution of epileptic seizures as the primary endpoint, as only 10% to 15% of patients suffer from them.

We chose VABS as the primary endpoint, as it has been evaluated in clinical trials on neurodevelopmental disorders, to assess the changes experienced by patients/families in their daily lives.[18] Nevertheless, in the absence of national or international consensus on the scales to be used in clinical trials aimed at demonstrating an improvement in patients with neurocognitive disorders, we have chosen to use a battery of scales, all addressing complementary domains, appropriate to the age, cognitive level, ability of the patients to concentrate and the time constraints between two assessments. We believe that the results of this trial will provide useful information for future clinical trials targeting neurodevelopmental pathologies. We added a simplified paradigm matrix stimuli especially designed by the expert team to try to identify fine points of improvement in clinical trials

that would be difficult to demonstrate with conventional scales.[23] Although we have no certainty about the possibility of achieving a reduction in brain volume, we felt it is important to assess this. Therefore, a volumetric MRI will be performed at the beginning of the study and at the end of the treatment. Given the poor knowledge of the prevalence of spinal cord abnormalities in MCAP, spinal cord MRI was added to the protocol. Assessing the quality of life as well as the effect of alpelisib on other non-brain manifestations of the disease was also planned.

The passage of alpelisib through the blood-brain barrier has only been hypothesised based on the observation of a reduction in the size of brain metastases in women with breast cancer or an improvement in epileptic seizures. It is, therefore, necessary to assess and quantify the passage of alpelisib into the CSF, in relation with the plasmatic dosage. This will help establish a correlation between the plasma concentration and that of the CSF, possibly allowing therapeutic monitoring on the basis of plasma concentrations alone.[24]

The SESAM trial also benefits from the accumulated experience of our previous trials, one with mTOR inhibitor sirolimus, the other with taselisib and another PI3Kα-specific inhibitor.[25 26] In particular, conducting this trial as part of a well-established network with investigators from local centres, enabling some of the follow-up visits to be carried out close to patients' homes, improves acceptability and ensures that the trial runs smoothly.

In addition, using this two-period design which allows all patients to be treated, we aim to demonstrate that a rigorous methodology can be applied in clinical trials in rare diseases, with high-quality standards while preserving the acceptability of the trial's burden for the patient. Based on our preliminary data in CLOVES, we will enhance knowledge relating to the efficacy and side-effect profile associated with long-term treatment with *PI3K* pathway inhibition and determine the effectiveness of treatment across an expanded number of PROS. Considering the pathological overlap deriving from the common feature of *PIK3CA* upregulation, our work may also inform future transversal therapeutic strategies in the context of a larger group of diseases.

Datasharing

All requests for the study's data will be considered by the SESAM trial steering committee.

Trial status

Recruitment is completed (last patient included in May 2024), and follow-up is ongoing until April 2026.

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Contributors ML is the guarantor for the overall content. LF and VB PV initiated this study. LF, ML and MB designed the study. ML has written this manuscript. LF, MB, AM, AE, AG, CR, AR, RL, NH, NB, AC, LG, MC, PK, JC, GC, NBH, AC, MC and CF (sponsor), and Novartis Pharmaceuticals (sponsor) reviewed the manuscript. All authors read and approved the final manuscript.

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Competing interests A patent application ('BYL719 (alpelisib) for the use in the treatment of PIK3CA-related overgrowth spectrum' #WO2017140828A1) has been filed by INSERM (Institut National de la Santé et de la Recherche Médicale), Centre National De La Recherche Scientifique (CNRS), Université Paris Cité and Assistance Publique-Hôpitaux De Paris (AP-HP) for the use of BYL719 (alpelisib) in the treatment of PIK3CA-related overgrowth spectrum (PROS/CLOVES syndrome). Dr Canaud is the inventor. This patent is licensed to Novartis Pharmaceutical. ML has received consulting fees from Novartis Pharmaceutical. GC receives or has received consulting fees from Novartis Pharmaceutical, Fresenius Medical Care, Vaderis, Alkermes, IPSEN and BridgeBio.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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