An Open-Label, Single Arm Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Leniolisib in Pediatric Patients (Aged 4 to 11 Years) With APDS (Activated Phosphoinositide 3-Kinase Delta Syndrome) Followed By an Open-Label Long-Term Extension

Published: 06-10-2022
Last updated: 29-04-2024

Objective Endpoint• To assess the clinical safety and tolerability of leniolisib in pediatric patients (aged 4 to 11 years) with APDS• Incidence of treatment-emergent AEs (TEAEs), SAEs, and AEs leading to discontinuation of study drug• Change from…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immune system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON53548

Source
ToetsingOnline

Brief title
A Study in Pediatric Patients (Aged 4 to 11 Years) with APDS

Condition

- Immune system disorders congenital

Synonym
Activated PI3Kδ syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Pharming Technologies b.v.
Source(s) of monetary or material Support: By the sponsor.

Intervention

Keyword: ADPS, Efficacy, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

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Secondary outcome

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Study description

Background summary

Activated PI3Kδ syndrome is an ultra-rare, genetic, life-threatening disorder of the immune system classified within a group of disorders called primary immune deficiencies (PIDs). Activated PI3Kδ syndrome 1 (APDS1) was also known as p110δ-activating mutations causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI) following its characterization (Lucas 2014).
Activated PI3Kδ syndrome is caused by mutations in the gene PIK3CD (type 1 APDS, APDS1, or PASLI-CD) or PIK3R1 (type 2 APDS, APDS2, or PASLI R1) that activate PI3Kδ (Michalovich 2018). The role of genetic variation of phosphoinositide 3-kinase (PI3K) coding genes in children with defects in B*cell immunodeficiency was first described in 2006 (Jou 2006) with the full PI3Kδ syndrome being first described in 2013 (Angulo 2013).
As with other PIDs, the majority of patients with APDS show symptoms and manifestations before the age of 18 years, although,

there are some manifestations that are recognized when patients are adults. Although the age of clinical onset can vary widely, most patients present with symptoms early in childhood. Due to the wide phenotypic variation and lack of consistent clinical diagnostic criteria in APDS, genetic testing showing the characteristic mutations are the current standard for accurate diagnosis.

In a systematic review involving the largest group of patients described so far (n=243), half of the patients were younger than 12 years of age when described in literature (n=213), with a median age at diagnosis of 10.0 years (range: 5.0 to 19.0) and a median age of symptom onset being 1.66 years (range: 0.58 to 3.0) (Jamee 2019). These data show that patients had a significant delay in diagnosis of 7.0 years (range: 3.4 to 14.0). In this analysis, 74% of the patients were APDS1 and 26% were APDS2; a positive family history was reported in 38.6%. Diagnostic testing for APDS is often only initiated when specialized medical treatment is required; unfortunately, this is often preceded by many years of severe clinical manifestations without specific diagnosis. This period of delay may shorten in the future as awareness among specialized physicians grows.

A mean age at onset of 1.66 (range: 0.6 to 3.0) years (n=111) has been reported, with recurrent respiratory infections starting at a median age of 1.2 (range: 0.6 to 2.0) years (n=36). Of the 103 patients for whom survival data was available, 14 (12%) had died from malignancy, bowel perforation, sepsis, multiple organ failure, or pulmonary hemorrhage. Infections occurred early in life (before 1 year of age) while enteropathy, lymphoproliferation, autoimmunity, and malignancy occurred somewhat later at median ages of 5 (range: 1 to 18), 3 (range: 1 to 6), 10.5 (range: 6.0 to 15.0), and 18 (range: 13 to 24) years, respectively (Jamee 2019). The phenotypic expression of APDS by APDS1 and APDS2 shows some variability. Activated PI3Kδ syndrome 1 shows increased presence of hepatomegaly, bronchiectasis, and sinusitis. Activated PI3Kδ syndrome 2 shows increased presence of lymphadenopathy, pneumonia, failure to thrive, neurodevelopment delay, and malignancy (Jamee 2019). In a cohort study, it was calculated that APDS2 patients have a 78% risk of developing a lymphoid malignancy by the age of 40 years (Elkaim 2016).

Common clinical hallmarks of the disease include recurrent sinopulmonary infections, severe or persistent viral infections, autoimmunity (eg, cytopenia, arthritis, enteropathy) and chronic benign lymphoproliferation with increased risk of developing lymphomas. Clinical and immunological features can range from asymptomatic or rarely symptomatic patients to more severe and life-threatening forms. Growth retardation and neurodevelopmental delay are frequently noticed in children with APDS (Elkaim 2016, Jamee 2019, Condliffe 2018). A total of 28% of patients with an established

primary diagnosis were initially diagnosed with hyper immunoglobulin (Ig) M syndrome with a history of chronic infections beginning in the first year of life (n=11) (Jamee 2019). Nearly half of all APDS patients who develop bronchiectasis in their disease course have no reported history of pneumonias. Malignancy can appear later in the disease course and most commonly presents as diffuse large B cell lymphoma (Jamee 2019). The manifestations of APDS are variable, even within families carrying the same mutation, ranging from a few isolated cases of seemingly symptomless adult patients to children with primary antibody deficiency and/or early onset recurrent respiratory infections with bronchiectasis to others suffering from lymphoproliferation, autoimmunity, or malignancy. A pattern is emerging of onset in early childhood in most cases, first with excess infections and respiratory disease, then lymphoproliferation and autoimmunity, and finally malignancy.

Currently, there are no approved therapies for APDS and no available targeted therapies that normalize the hyperactive PI3Kδ pathway in APDS. Current medical practice constitutes mainly of preventive, supportive, or symptomatic treatment tailored to the individual patient. Currently available therapies are not specific to the underlying biology of APDS. The available symptomatic and preventive treatments only address part of the manifestation of APDS. Hematopoietic stem cell transplantation (HSCT) is only an option for a small subset of APDS patients (12.8%), but carries significant risks, including mortality in 10% to 20% of patients (Jamee 2019, Nademi 2017, Okano 2019). The estimated graft failure-free survival rate in a series of 27 APDS patients receiving HSCT at a median age of 12 years (range 2 to 66) is 68% at 2 years (Dimitrova 2020).

There is an unmet need for therapies targeting the PI3K pathway that have the potential to mitigate progression and disease burden by inhibiting the root cause of the disease manifestations versus the current standard of care. Therapies targeting the underlying biology of APDS are anticipated to improve the clinical outcomes and quality of life for patients with APDS.

Leniolisib (previously known as CDZ173 and now referred to as PH-E6) is an orally available, small molecule inhibitor of p110δ that inhibits the production of PIP3. Leniolisib has been investigated for safety and tolerability in a first-in-human study (CCDZ173X2101) and 2 drug drug interaction studies (CCDZ173X2102 and CCDZ173X2104). Healthy volunteers were exposed to single ascending doses up to 400 mg and multiple doses up to 140 mg BID for 15 days. Leniolisib has also been investigated in a study (CCDZ173X2203) in patients with primary Sjögren*s syndrome (pSS). In addition, leniolisib is being evaluated in Phase 3 studies

(CCDZ173X2201 and CCDZ173X2201E1) in adolescent (>=12 years of age) and adult patients with APDS. The completed study
CCDZ173X2201 consists of 2 parts. Part I was an open-label, within-patient, up-titration dose escalation study designed to establish
the safety and PK of leniolisib in the target population, as well as to select
the optimal dose to be tested in Part II. Part II was
designed to assess efficacy and safety of leniolisib in this population. The
ongoing study CCDZ173X2201E1 is an open-label, non-randomized, safety, tolerability, efficacy, and PK study to extend active oral treatment with
leniolisib 70 mg BID to those adolescent
and adult patients with APDS who participated in study CCDZ173X2201 or who were previously treated with PI3Kδ inhibitors other
than leniolisib; treatment with leniolisib will last up to 6 years for an
individual patient.
Given the specificity of leniolisib to selectively inhibit the PI3K class IA
p110δ subunit, which harbors the gain-of-function mutation
driving APDS, leniolisib specifically targets the causative factor resulting in
the pathogenesis of APDS, and thereby may provide
effective treatment for this newly described disease with a significant unmet medical need. This will be the first study to evaluate
leniolisib in children (aged 4 to 11 years) with mutations of either the PIK3CD (APDS1) or PIK3R1 (APDS2) gene confirming APDS.
Further information regarding the nonclinical and clinical data for leniolisib
is provided in the Investigator*s Brochure.

Study objective

Objective Endpoint
• To assess the clinical safety and tolerability of leniolisib in pediatric
patients (aged 4 to 11 years) with APDS
• Incidence of treatment-emergent AEs (TEAEs), SAEs, and AEs leading to
discontinuation of study drug
• Change from baseline in clinical laboratory test results (hematology, blood
chemistry, urinalysis)
• Change from baseline in vital signs
• Change from baseline in physical examination findings
• Change from baseline in electrocardiograms (ECGs)
• Change from baseline in growth and physical development
• To assess the efficacy of leniolisib in pediatric patients (aged 4 to 11
years) with APDS
• Reduction in lymphadenopathy as measured by MRI or low-dose CT at end of 12 weeks of treatment
• Immunophenotype assessed by changes from baseline in the percentage of naïve B cells to total B cells to end of 12 weeks of
treatment

Study design

This study is a 2-part, prospective, open-label, single arm, multicenter study to evaluate the safety, tolerability, PK, PDx, and efficacy of leniolisib in at least 15 pediatric patients (aged 4 to 11 years) with mutations of either the PIK3CD (APDS1) or PIK3R1 (APDS2) genes confirming APDS. At least 4 patients <6 years of age will be enrolled. Part I will consist of a 12-week period to assess the safety and efficacy of treatment with leniolisib. Part II will consist of a 1-year, long term, safety follow-up extension, with a possible interim analysis. The leniolisib doses to be used in study were selected based on safety, tolerability, PK, and PDx data from the adult Phase 2/3 study, as well as PK modeling data (see Section 3.4 for more details.) In both parts of the study, leniolisib will be administered orally based on body weight. Doses will range from 20 to 70 mg BID (resulting in total daily doses ranging from 40 to 140 mg per day). In Part I of the study, patients will stay on the same dose based on their weight at baseline throughout the 12-week treatment period. In Part II, doses will be adjusted as needed for changes in weight at each scheduled study visit. Safety and tolerability will be assessed. Safety will be assessed from start of treatment through 28±5 days following completion of treatment. Safety assessments will include physical examinations, vital signs (body temperature, blood pressure, and pulse rate), standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), AE and SAE monitoring, and cardiac safety, which will be monitored by means of 12-lead ECGs. Further assessments will include the PedsQL Child Self Report Health Related Quality of Life Questionnaire for patients age 5 to 11 years, the PedsQL Parent Proxy Report Health Related Quality of Life Questionnaire for patients age 4 years, and PGA. Tablet tolerability will be assessed. Population PK will be assessed, using a sparse sampling technique to minimize burden. During each part of the study, patients will be randomized to 1 of 3 PK sampling groups. In each group, up to 4 blood samples will be collected on any 1 day during Part I and 1-year (Part II) treatment periods. Efficacy will assess reduction of lymphadenopathy and immunophenotype. Reduction of lymphadenopathy will be measured by the SPD in the index lesions selected as per the Cheson methodology from imaging. For imaging, sites may choose either of the 2 imaging modalities (MRI or CT) as per clinical practice and local regulations (see imaging review charter). Baseline and end of treatment assessments must be done using the same imaging modality. The immunophenotype efficacy will be assessed by change from baseline in the percentage of nai*ve B cells to total B cells. For ongoing or as needed safety review, a Data Monitoring Committee will be established. See Section 10.3, Appendix 3 for further details. If an epidemic or pandemic (eg, COVID-19 pandemic) limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls or virtual contacts (eg, teleconsult) to the patient, depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the patient to visit the site again.

Intervention

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Study burden and risks

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

• Patient is male or female and between the age of 4 to 11 years old at time of the first study procedure. Females should be of nonchildbearing potential at screening. • Patient weighs >=13 kg and <45 kg at baseline. • Patient has

confirmed PI3Kδ genetic mutation of either the PIK3CD (APDS1) or PIK3R1 (APDS2) gene. • Patient has at least 1 measurable nodal lesion on magnetic resonance imaging (MRI)/low-dose computed tomography (CT). • Patient has nodal or extranodal lymphoproliferation and clinical findings consistent with APDS (eg, a history of repeated oto-sino-pulmonary infections and/or organ dysfunction consistent with APDS). • Patient has the ability to ingest unaltered study-related medications without difficulty.

Exclusion criteria

• Patient has previous or concurrent use of immunosuppressive medication such as: a. An mTOR inhibitor (eg, sirolimus, rapamycin, everolimus) or a PI3Kδ inhibitor (selective or non-selective PI3K inhibitors) within 6 weeks prior to first dose. i. Short-term use for up to a total of 5 days is allowed but only up to 1 month prior to enrollment in the study. b. B cell depleters (eg, rituximab) within 6 months prior to first dose of study medication. i. If patient has received prior treatment with a B cell depleter, absolute B lymphocyte counts in the blood must have regained normal values. c. Belimumab or cyclophosphamide within 6 months prior to first dose of study medication. d. Cyclosporine A, mycophenolate, 6-mercaptopurine, azathioprine, or methotrexate within 3 months prior to first dose of study medication. e. Systemic glucocorticoids above a dose equivalent to either >=2 mg/kg of body weight or >=20 mg/day of prednisone/prednisolone or equivalent. f. Other immunosuppressive medication where effects are expected to persist at start of dosing of study medication. • Patient has a history or current diagnosis of electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study such as: a. History of familial long QT syndrome or known family history of Torsades de Pointes. b. Concomitant clinically significant cardiac arrhythmias, eg, sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular block without a pacemaker. c. Resting QTc (Fridericia preferred, but Bazett acceptable) >460 msec if the measurement is confirmed with an additional ECG repeated as soon as possible. d. Concomitant use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study. • Patient is currently using a medication known to be strong inhibitor or moderate or strong inducer of isoenzyme CYP3A (see Table 2), if treatment cannot be discontinued or switched to a different medication prior to starting study treatment. • Patient is currently using medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index (drugs whose exposure- response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns [eg, Torsades de Pointes]). e. Patient is currently using medications known to be organic anion transporter protein (OATP)1B1, OATP1B3, and breast cancer resistance protein (BCRP) substrates

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-10-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n/a
Generic name:	Leniolisib

Ethics review

Approved WMO

Date:	06-10-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	24-04-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	21-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2022-001624-14-NL
CCMO	NL82692.078.22