# A Phase 2, Multicenter, Multinational, Open-Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of ORGN001 (formerly ALXN1101) in Pediatric Patients with Molybdenum Cofactor Deficiency (MoCD) Type A Currently Treated with Recombinant Escherichia coli-derived Cyclic Pyranopterin Monophosphate (rcPMP)

Published: 03-01-2014
Last updated: 24-04-2024

Primary:• To evaluate the safety of ORGN001 (formerly ALXN1101) over the first 6 months of treatmentSecondary:• To characterize the pharmacokinetics (PK) of increasing doses of ORGN001 (formerly ALXN1101) • To evaluate the effect of ORGN001 (...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Congenital and hereditary disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON55625

**Source**
ToetsingOnline

**Brief title**
ALXN1101-MCD-201

## Condition

- Congenital and hereditary disorders NEC

**Synonym**
and aldehyde oxidase, Combined deficiency of sulfite oxidase, xanthine dehydrogenase

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Origin Biosciences, Inc.
**Source(s) of monetary or material Support:** Origin Biosciences;Inc.

## Intervention

**Keyword:** Efficacy, Molybdenum Cofactor Deficiency, Pediatric Patients, Safety

## Outcome measures

### Primary outcome

Safety over the first 6 months of treatment

### Secondary outcome

Safety:

• Incidence and severity of adverse events (AEs) and serious adverse events

(SAEs)

• Incidence of clinical laboratory abnormalities

• Change from baseline in clinical laboratory assessments

• Change from baseline in clinical findings from physical examination

• Change from baseline in vital sign measurements

• Change from baseline in EEG results

Efficacy:

• Change from baseline in urine and blood SSC levels

• Change from baseline in clinical findings from neurologic examination

• Change from baseline in age-appropriate motor and cognitive assessments (Bayley Scales of Infant Development-Third Edition [Bayley-III], The Gross Motor Function Classification System [GMFCS], Wechsler Preschool and Primary Scale of Intelligence [WPPSI])

• Change from baseline in seizure frequency

• Change from baseline in neuroimaging

• Changes in growth parameters (body weight, body length, head circumference)

• Change from baseline in feeding patterns

Pharmacokinetic:

• PK parameters of ORGN001 (formerly ALXN1101) including, but not limited to, maximum observed plasma concentration (Cmax), time to maximum observed plasma concentration (tmax), area under the plasma concentration-time curve (AUC) and if possible, terminal half-life (t*), and dose linearity

Exploratory:

• Change from baseline in MoCD-associated urine and blood biomarker levels including, but not limited to, uric acid and xanthine

# Study description

**Background summary**

Molybdenum cofactor deficiency (MoCD) is a rare, life-threatening, autosomal recessive, inborn error of metabolism characterized by disruption of the metabolic pathway for production of molybdenum cofactor (MoCo), which is essential for the function of the following 3 critical enzymes: sulfite oxidase (SO), xanthine dehydrogenase, and aldehyde oxidase. While all 3 enzymes are dependent on MoCo, the loss of SO activity is exclusively responsible for the severe and rapidly progressive neurologic damage seen in MoCD.
Little documentation is available regarding the prevalence of MoCD since the first recognition of the condition in 1978. MoCD is estimated to affect less than 200 patients worldwide. While there is incomplete information on the natural history of MoCD, affected individuals usually present as neonates with severe symptoms such as intractable seizures, burst-suppression electroencephalogram (EEG), metabolic acidosis, exaggerated startle reactions, axial hypotonia, limb hypertonia, and feeding difficulties. Neuronal damage is severe and is rapidly progressive as a result of accumulation of toxic levels of sulfite in the brain. Death commonly occurs in the neonatal period, and patients who survive that period develop a severe static encephalopathy and developmental delay due to central nervous system (CNS) injury including subcortical cystic cavitation, hydrocephalus, diffuse cortical atrophy, and basal ganglia injury. At present, there is no cure.
Although there are 3 types of MoCD, two-thirds of MoCD patients have Type A, which is due to a mutation in the MOCS1 gene localized on 6p21.3. In MoCD Type A, the first of the four synthetic steps in the formation of MoCo is interrupted, and guanosine triphosphate (GTP) cannot be converted into cyclic pyranopterin monophosphate (cPMP). Diagnosis of MoCD Type A is based on clinical presentation, biochemical phenotype (such as elevated urinary sulfite and/or S sulfocysteine [SSC], and low or absent uric acid in the urine or plasma), and diagnosis is then confirmed by genetic testing.
ORGN001 (formerly ALXN1101) provides a therapeutic approach for the treatment of MoCD Type A by restoring the MoCo biosynthesis. Results of preclinical pharmacology studies with ORGN001 (formerly ALXN1101) suggest that the metabolic derangement in MoCD Type A could be corrected by administration of synthetic cPMP, resulting in restoration of enzymatic activity and thus, correction of the metabolic pathways that would otherwise lead to the accumulation of toxic metabolites causing CNS injury. These results are supported by data obtained in pediatric patients with MoCD Type A treated with a recombinant Escherichia coli-derived cPMP product (rcPMP) from Colbourne Pharmaceuticals GmbH (Colbourne), which has been administered on a named-patient basis following request from their individual physicians. Published individual case reports suggest that intravenous (IV) administration of rcPMP restores MoCo -dependent enzyme activities as evidenced by the reduction in levels of biomarkers of the disease (e.g., SSC in urine) and improvement in neurologic outcome. This study is designed to evaluate the safety and efficacy of escalating doses of ORGN001 (formerly ALXN1101) in pediatric patients with MoCD Type A currently treated with rcPMP.

## Study objective

Primary:
• To evaluate the safety of ORGN001 (formerly ALXN1101) over the first 6 months of treatment

Secondary:
• To characterize the pharmacokinetics (PK) of increasing doses of ORGN001 (formerly ALXN1101)
• To evaluate the effect of ORGN001 (formerly ALXN1101) on urine and blood SSC levels
• To evaluate the effect of ORGN001 (formerly ALXN1101) on neurologic, motor, and cognitive functions
• To evaluate the effect of ORGN001 (formerly ALXN1101) on CNS structure
• To evaluate the long-term safety of ORGN001 (formerly ALXN1101)

Exploratory:
• To describe the effect of ORGN001 (formerly ALXN1101) on MoCD-associated urine and blood biomarker levels including, but not limited to, uric acid and xanthine

## Study design

This Phase 2, multicenter, multinational, open-label, dose-escalation study is designed to evaluate the safety and efficacy of ORGN001 (formerly ALXN1101) administered to infants and children with MoCD Type A currently treated with rcPMP. Eligible patients will be identified through named-patient use with rcPMP. This study will include a screening period (Days -21 to Day -1), a 6-month Initial Treatment Period which includes escalating doses of ORGN001 after the first 2 months of treatment with ORGN001 (Day 1 [first dose of study drug] to Day 180), and an Extension Period (after Day 180).

## Intervention

ORGN001 (formerly ALXN1101) is a synthetic form of cPMP. Patients will begin IV infusions of ORGN001 (formerly ALXN1101) at the same dose as their current dose of rcPMP. After the first 2 months of treatment with ORGN001 (formerly ALXN1101) , if the patient*s clinical, PK, and safety assessments permit (including absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 (formerly ALXN1101) will increase every month by no more than 240 µg/kg/day increments until either 1) Day 180, 2) the patient reaches a dose that is not tolerated, or 3) the patient*s exposure approaches or exceeds that of the NOAEL in toxicology species, whichever comes first. Unscheduled dose adjustments of ORGN001 (formerly ALXN1101) are possible based on recommendation by the SRC. The SRC chair will also convine the DMC if a dose escalation is being considered, or will notify the DMC if the dose is decreased. After dose

escalation is complete, the patient can be returned to the prior dose based on the patient*s clinical status at the discretion of the treating physician after consultation with the SRC. All doses will be administered by IV infusion over approximately 10 to 15 minutes and infusion times would increase proportionally with increasing dose.
ORGN001 (formerly ALXN1101)is supplied as a sterile, non-pyrogenic, white to slightly yellow lyophilized powder in a 10 mL vial to be reconstituted using sterile Water for Injection prior to administration.

**Study burden and risks**

Risk/benefit assessment:

MoCD Type A is a rare, life-threatening, autosomal recessive, inborn error of metabolism. Within a few hours to days after birth, newborn infants with MoCD Type A present a severe clinical picture with profound and progressive neuronal damage. Death may occur in the neonatal period. Currently, no approved therapy is available in the EU for the treatment of patients with MoCD Type A. Treatment strategies for individuals with this disorder are only symptomatic and aim to provide relief of clinical manifestations of the disease and palliative care of the patient.
Because of the life-threatening and debilitating nature of the disease and lack of treatment, there is a significant need to provide safe and effective treatment for pediatric patients with MoCD Type A, which targets the underlying cause of the disease, the inability to synthesize MoCo from its precursor, GTP. Treatments, such as ORGN001 (formerly ALXN1101) , that aim to restore MoCo biosynthesis represent one of the most promising therapeutic interventions. Considering the identical molecular structures of ORGN001 (formerly ALXN1101) and rcPMP, the clinical results reported with rcPMP in the literature, together with the nonclinical results with ORGN001 (formerly ALXN1101), it is anticipated that ORGN001 (formerly ALXN1101) will benefit patients with MoCD Type A by correcting the metabolic derangement, reconstituting the synthesis of MoCo, and thus restoring SO enzymatic activity and reducing the levels of the toxic metabolites, sulfite and SSC.

# Contacts

**Public**
Origin Biosciences, Inc.

Park Plaza 75
Boston, MA 02116
US
**Scientific**

Origin Biosciences, Inc.

Park Plaza 75
Boston, MA 02116
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

## Inclusion criteria

1) Male of female patients with genetically confirmed diagnosis of MoCD Type A (MOCS1 mutation) and who are currently treated with rcPMP infusions.
2) Parent or legal guardian must have signed the informed consent form (ICF) prior to any study procedures.

## Exclusion criteria

Current or planned treatment with another investigational drug or device, with the exception of rcPMP treatment through Day -1

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 30-04-2015 |
| Enrollment: | 2 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Brand name: | N/A |
| Generic name: | cyclic pyranopterin monophosphate monohydrobromide dihydrate |

# Ethics review

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| Approved WMO Date: | 03-01-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 16-05-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 20-06-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

Approved WMO

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| Date: | 09-10-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 16-01-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 08-04-2015 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 09-07-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 04-02-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 25-05-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 22-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 21-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 22-12-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO | |

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|---|---|
| Date: | 05-01-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 21-07-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 27-07-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 14-01-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 08-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 09-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 23-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 22-01-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 06-03-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO | |

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| Date: | 31-08-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 17-09-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 13-08-2021 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 04-11-2021 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# 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 | EUCTR2013-002701-56-NL |
| ClinicalTrials.gov | NCT02047461 |
| CCMO | NL46997.042.13 |

# Study results

Results posted: 07-03-2023

**First publication**
01-01-1900