NCT Number: NCT02047461

Certain information within this protocol has been redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems.
- Other information as needed to protect confidentiality of BridgeBio Pharma, Sentynl Therapeutics, Inc., or their partners, or to otherwise protect the integrity of the clinical study.

ALXN1101-MCD-201

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)

Sponsor:	Origin Biosciences, Inc. [redacted] USA	**Former Sponsor:**	Alexion Pharma GmbH Giesshübelstrasse 30 8045 Zürich SWITZERLAND
IMP Name:	ORGN001	**Former IMP Name:**	ALXN1101
Sponsor Contact:	[redacted] Origin Biosciences, Inc. [redacted] USA [redacted]		
Medical Monitor:	[redacted] Origin Biosciences, Inc [redacted]		
Version:	8		
Date of Protocol:	03 January 2020 (Amendment 7)		
Amended:	Protocol Version 1.0 dated 08 August 2013 (Original) Protocol Version 2.0 dated 19 November 2013 (Amendment 1.0) Protocol Version 3.0 dated 27 January 2014 (Amendment 2.0) Protocol Version 4.0 dated 01 October 2015 (Amendment 3.0) Protocol Version 5.0 dated 09 December 2016 (Amendment 4.0) Protocol Version 6.0 dated 13 January 2017 (Amendment 5.0) Protocol Version 6.1 dated 23 November 2018 (Amendment 5.1) Protocol Version 7.0 dated 28 June 2019 (Amendment 6.0)		
IND Number:	117502		
EudraCT Number:	2013-002701-56		

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: 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)

PROTOCOL NUMBER: ALXN1101-MCD-201

[redacted] 03 Jan 2020
Date

Chief Medical Officer
Origin Biosciences, Inc.

[redacted] 03 January 2020
Date

Vice President, Regulatory Affairs
Origin Biosciences, Inc.

[redacted] 3 Jan 2020
Date

Senior Director, Clinical Operations
Origin Biosciences, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ORGN001 (formerly ALXN1101). I have read the ALXN1101-MCD-201 study protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to conduct the trial in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted]	Origin Biosciences, Inc. [redacted]
Responsible Physician	[redacted]	Origin Biosciences, Inc. [redacted]
Serious Adverse Event Reporting	[redacted]	[redacted]

SYNOPSIS

Name of Sponsor/Company: Origin Biosciences, Inc. (Origin); previously; Alexion Pharmaceuticals, Inc. (Alexion)

Name of Investigational Product: ORGN001 (formerly ALXN1101)

Name of Active Ingredient: Cyclic pyranopterin monophosphate monohydrobromide dihydrate

Title of Study: 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)

Study centers: This will be a multicenter, multinational study with approximately 5 investigational study centers.

Principal Investigator: TBD

Investigators: TBD

Studied period:	**Phase of development:**
6-Month Initial Treatment Period, followed by an Extension Period Estimated date first patient enrolled: February 2014 Estimated date last patient completed: The Extension Period is expected to last until ORGN001 is commercially available or development is stopped.	2/3

Study Rationale

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 sulfite oxidase (SO), [redacted] dehydrogenase, and aldehyde oxidase. While all 3 enzymes are dependent on MoCo, the loss of SO activity is responsible for the severe and rapidly progressive neurologic damage seen in MoCD.

The incidence of MoCD is estimated to be between 1/100,000 and 1/200,000 newborn babies worldwide (Schwahn 2015). Affected individuals usually present as neonates with severe symptoms such as intractable seizures, burst-suppression or multifocal electroencephalogram (EEG), exaggerated startle reactions, axial hypotonia, limb hypertonia, and feeding difficulties. Neuronal injury is severe and is rapidly progressive as a result of accumulation of toxic levels of sulfite in the brain and subsequent formation of S-sulfocysteine (SSC). 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 4 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 and biochemical phenotype (such as elevated urinary sulfite and/or SSC, and low or absent uric acid in the urine or plasma), and diagnosis is then confirmed by genetic testing.

ORGN001 (cyclic pyranopterin monophosphate monohydrobromide dihydrate), provides a therapeutic approach for the treatment of MoCD Type A by restoring the MoCo biosynthesis. Results of preclinical pharmacology studies with ORGN001 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) [redacted]. 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 (eg, SSC in urine) and improvement in neurologic outcome. This study is designed to evaluate the safety and efficacy of escalating doses of ORGN001 in pediatric patients with MoCD Type A currently treated with rcPMP.

Objectives

Primary:

To evaluate the safety of ORGN001 over the first 6 months of treatment

Secondary:

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

[redacted]

Endpoints

The following endpoints will be measured over the first 6 months of treatment and over the entire treatment period:

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 and Toddler 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:

- Pharmacokinetic parameters of ORGN001 including, but not limited to, maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC) and if possible, terminal half-life ($t_{½}$) and dose linearity

[redacted]

Methodology:

This Phase 2, multicenter, multinational, open-label, dose-escalation study is designed to evaluate the safety and efficacy of ORGN001 administered to infants and children with MoCD Type A currently treated with rcPMP. [redacted] 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 ORGN001 treatment (Day 1 [first dose of study drug] to Day 180), and an Extension Period (post Day 180). A patient may be discontinued once ORGN001 is registered and available as a treatment for MoCD Type A in the region where the patient resides or is receiving treatment (in accordance with country--specific requirements).

Screening evaluations will be performed at any time during the Screening Period before the first dose of ORGN001. Enrolled patients will attend at least 2 study visits in order for baseline data to be obtained. During the Screening Period, patients will continue to receive daily IV infusions of their current rcPMP treatment.

During the 6-Month Initial Treatment Period, starting on Day 1, patients will begin IV infusions of ORGN001 at the same dose as their current dose of rcPMP, approximately 24 hours after their last treatment with rcPMP. No further treatments with rcPMP will be allowed during the study. Patients [redacted].

[redacted] patients will continue to receive daily infusions of ORGN001 at home [redacted] and will attend multiple study visits for safety, efficacy, pharmacodynamic (PD), and PK assessments through Day 180. After the first 2 months of treatment with ORGN001, if the patient's clinical, PK, and safety assessments permit (including the absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 will increase every month [redacted] based on the patient's clinical response, safety laboratory assessments, and when appropriate, ORGN001 exposure data. Dose escalation will continue until either 1) Day 180, 2) the patient reaches a dose that is not tolerated, 3) the patient's exposure exceeds that of the no observed adverse effect level (NOAEL) AUC [redacted], or 4) the patient's exposure following dose escalation is predicted to exceed that of the NOAEL [redacted], whichever comes first. After the 6-Month Initial Treatment Period, patients will enter the Extension Period and continue to receive uninterrupted daily dosing of ORGN001 at their final tolerated dose based on the dose escalation. During the Extension Period, patients who were de-escalated from the final tolerated dose for reasons other than safety or PK considerations may be re-escalated up to their maximally tolerated dose. After dose escalation is complete, the patient can be returned to a prior dose based on the patient's clinical status at the discretion of the treating physician after consultation with the Safety Review Committee (SRC). Patients who prematurely discontinue from the study will attend a Safety Follow--up Visit [redacted] and return to the care of their treating physician.

In order to monitor patient safety of ORGN001, patient data will be reviewed daily by the Principal Investigator (PI) or designee during the first 2 weeks following initiation of ORGN001. In addition, an SRC, [redacted] will review all available clinical data after each patient has completed the first 2 weeks of treatment with ORGN001, prior to each patient's scheduled dose escalations [redacted] and at any other time during the study as requested by the PI or Sponsor. Based on the review of the available data, which may include laboratory data, clinical assessments, neuroimaging (if needed), and exposure data, the SRC, in consultation with an independent, external Data Monitoring Committee (DMC), may recommend stopping, increasing, decreasing, or maintaining the dose of ORGN001. [redacted]

In addition to the scheduled dose escalations, a PI may identify the need for a dose adjustment in a patient based on the available data, including study drug-related AEs and/or changes in clinical parameters, and will convene the SRC to determine if an unscheduled dose adjustment is warranted. Blood and urine samples will be collected for PD and PK assessments on the first Day the adjusted dose is administered. PD and safety laboratory assessments will be repeated [redacted] at the [redacted] Follow--up Visit.

In addition, the SRC chair [redacted] will request that the DMC convene if any of the criteria to hold dose escalation occur, or at any time during the study, as needed.

Number of patients (planned):

At least 4 patients with MoCD Type A will be enrolled in the study. The actual sample size will depend on the number of eligible patients currently treated with rcPMP.

Diagnosis and main criteria for inclusion

Inclusion criteria:

Patients must meet all of the following criteria to be enrolled in the study:

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

Exclusion criterion:

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

Investigational product, dosage and mode of administration:

ORGN001 is a synthetic form of cPMP. Patients will begin IV infusions of ORGN001 at the same dose as their current dose of rcPMP. After the first 2 months of treatment with ORGN001, if the patient's clinical, PK, and safety assessments permit (including the absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 will increase every month [redacted] until either 1) Day 180, 2) the patient reaches a dose that is not tolerated, 3) the patient's exposure exceeds that of the no observed adverse effect level (NOAEL) AUC [redacted], or 4) the patient's exposure following dose escalation is predicted to exceed that of the NOAEL [redacted], whichever comes first. Unscheduled dose adjustments of ORGN001 are possible based on recommendation by the SRC. During the Extension Period, patients who were de-escalated from the final tolerated dose for reasons other than safety or PK considerations may be re- escalated up to their maximally tolerated dose. After dose escalation is complete, the patient can be returned to a 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 at a rate of 1.5 mL/minute.

ORGN001 is supplied as a sterile, [redacted] white to slightly yellow lyophilized powder [redacted] to be reconstituted using sterile Water for Injection prior to administration.

Duration of treatment:

After a 3-week Screening Period, ORGN001 will be administered once daily during the 6-Month Initial Treatment Period, followed by daily treatment in the Extension Period.

Reference therapy, dosage and mode of administration: None

Criteria for evaluation

Safety variables:

Treatment-emergent AEs, SAEs, clinical findings from physical examination, clinically significant laboratory abnormalities (serum chemistry, hematology, urinalysis), changes from baseline in laboratory analyses, EEGs, or vital signs (heart rate, respiratory rate, blood pressure, temperature), concomitant medications/procedures

Efficacy variables:

Changes in urine and blood SSC levels (urine levels normalized to urinary creatinine), clinical findings from neurologic examination, motor and cognitive assessment results (Bayley-III, GMFCS -expanded and revised, WPPSI), incidence of seizures (if present), findings from neuroimaging (magnetic resonance imaging scan), growth parameters (body weight, body length, head circumference), changes in feeding patterns

Pharmacokinetic variables:

- Cmax, tmax, AUC, t½, and dose linearity

[redacted]

Statistical methods:

The statistical analysis of all safety and efficacy parameters will be conducted on all patients who receive at least 1 dose of ORGN001. All data collected in this study will be documented using summary tables, figures and patient data listings. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum) will be presented.

Safety:

The incidence of treatment-emergent AEs and SAEs will be summarized by System Organ Class (SOC) and Preferred Term overall, by severity, and by relationship to study drug. Changes from baseline in vital signs, laboratory assessments (chemistry, hematology, and urinalysis) will be summarized. Shifts from baseline in laboratory assessments as well as physical examination findings will be summarized for the different time points.

Efficacy:

Changes from baseline in urine and blood SSC levels and percentage changes from baseline to the study time points will be summarized. Observed values and changes in Bayley-III cognitive, gross, fine motor scaled scores and cognitive and motor composite scores will be summarized. The frequency of seizures will be summarized. Shifts from baseline in clinical findings from neurologic examinations and neuroimaging findings will be presented for the different time points. Growth parameters (body weight, body length, and head circumference) will be converted to age-adjusted z-scores and summarized over time. Graphical displays will be presented as appropriate.

Pharmacokinetics:

Plasma concentration versus time profiles will be graphically summarized. Noncompartmental PK parameters such as C_{max}, t_{max}, AUC, and $t_{½}$ will be determined if possible, and, dose linearity will be explored. Plasma concentration and PK parameter summaries will include descriptive statistics, as appropriate. [redacted]

Additional details for statistical analyses will be described in the statistical analysis plan.

SUMMARY OF CHANGES

Section	Description of Change
1.3 Risk/Benefit Assessment	Additional text: "*In vitro* and preclinical studies have identified that ORGN001 has phototoxic potential. Patients and caregivers are instructed to avoid direct sunlight and to use precautions when exposed to the sun. Protective measures include wearing of sunglasses, a hat, long sleeved shirts, long pants and the use of protective sunscreen."

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation	Definition
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon nuclear magnetic resonance spectroscopy
^{31}P NMR	Phosphorous nuclear magnetic resonance spectroscopy
AE	Adverse event
Alexion	Alexion Pharma GmbH
AUC	Area under the plasma concentration-time curve
BP	Blood pressure
Bayley-III	Bayley Scales of Infant and Toddler Development-Third Edition
°C	Degrees Celsius
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
Colbourne	Colbourne Pharmaceuticals GmbH
cPMP	Cyclic pyranopterin monophosphate
CRF	Case Report Form
CT	Computed tomography
CYP 450	Cytochrome P450
DMC	Data Monitoring Committee
EC	Ethics Committee
E. coli	*Escherichia coli*
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EMLA	Eutectic mixture of local anesthetics
EOI	End of infusion
EOS	End of study
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMFCS	Gross Motor Function Classification System
GMP	Good Manufacturing Practice
GTP	Guanosine triphosphate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometric detection
MoCD	Molybdenum cofactor deficiency
MedDRA	Medical Dictionary for Regulatory Activities
MoCo	Molybdenum cofactor
MPT	Molybdopterin
MRI	Magnetic resonance imaging
MS	Mass spectroscopy
MSDS	Material Safety Data Sheet
N	Normal
NOAEL	No observed adverse effect level
Origin	Origin Biosciences, Inc.
PD	Pharmacodynamics

PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
RBC	Red blood cell
rcPMP	Recombinant *E. coli*-derived cPMP
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SO	Sulfite oxidase
SOC	System Organ Class
SRC	Safety Review Committee
SSC	S-sulfocysteine
$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum observed plasma concentration
UK	United Kingdom
US	United States (of America)
UV	Ultraviolet (spectroscopy)
WBC	White blood cell
WHODrug	World Health Organization Drug Dictionary
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1 INTRODUCTION

1.1 Background

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 sulfite oxidase (SO), xanthine dehydrogenase, and aldehyde oxidase. While all 3 enzymes are dependent on MoCo, the loss of SO activity is responsible for the severe and rapidly progressive neurologic damage seen in MoCD.

The incidence of MoCD is estimated to be between 1/100,000 and 1/200,000 newborn babies worldwide (Schwahn 2015). Affected individuals usually present in the neonatal period with intractable seizures, burst--suppression or multifocal epileptic electroencephalogram (EEG), exaggerated startle reactions, axial hypotonia, limb hypertonia, and feeding difficulties (Johnson and Duran 2001; Kikuchi et al, 2012; Vijayakumr et al, 2011). Neuronal injury is severe and is rapidly progressive as a result of accumulation of toxic levels of sulfite in the brain and subsequent formation of S-sulfocysteine (SSC). 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 (Johnson and Duran 2001; Johnson et al, 1980).

Three types of MoCD have been described based on the genetic defect. Two-thirds of MoCD patients have Type A, which is due to a mutation in the MOCS1 gene localized on 6p21.3 and results in the interruption of the first of the 4 synthetic steps in the formation of MoCo; guanosine triphosphate (GTP) cannot be converted into cyclic pyranopterin monophosphate (cPMP). Diagnosis of MoCD Type A is based on clinical presentation (encephalopathy, seizures) and biochemical phenotype (elevated urinary sulfite and SSC, and low or absent uric acid in the urine or plasma). The diagnosis is then confirmed by genetic testing. At present, there is no approved therapy available and no cure.

A treatment targeting MoCo biosynthesis represents a possible therapeutic strategy to treat MoCD Type A. A cPMP substitution therapy is expected to reconstitute MoCo biosynthesis and restore SO levels, thereby reducing the levels of the neurotoxic compounds, sulfite and SSC.

1.2 Rationale for the Study

The previous sponsor, Alexion Pharma GmbH (Alexion) developed ORGN001 (formerly ALXN1101), a synthetic form of cPMP, which is a precursor molecule to MoCo, as a treatment for MoCD Type A. Responsibility for the development of ORGN001 for the treatment of MoCD Type A has been assumed by Origin Biosciences, Inc. ORGN001 provides a therapeutic approach for the treatment of MoCD Type A that is intended to restore MoCo biosynthesis. Results of preclinical pharmacology studies with ORGN001 suggest that the metabolic derangement in MoCD Type A could be corrected by administration of synthetic cPMP, resulting in restoration of enzymatic activity and thereby correction of the metabolic pathways that lead to the accumulation of toxic metabolites causing CNS injury.

In vitro, ORGN001 increased molybdopterin (MPT) synthesis and restored SO activity (Clinch et al, 2013). Additionally, in a mouse model of MoCD Type A (Lee et al, 2002), ORGN001 effectively rescued MOCS1$^{-/-}$ mice from premature death and effectively decreased the plasma SSC level. In [redacted] repeat dose-toxicity studies in adult rats and dogs, ORGN001

did not accumulate and had a short (<1 hour) half-life. ORGN001 was well tolerated and did not show evidence of toxicity at the highest possible dose tested [redacted]. In a [redacted] juvenile rat study, ORGN001 was also well tolerated [redacted]. ORGN001 did not show any genetic toxicity. ORGN001 produced no effects on the cardiovascular, neurobehavioral, or pulmonary functions at the doses tested. [redacted]

The use of ORGN001 as a potential treatment for MoCD Type A is supported by preliminary clinical evidence obtained from MoCD pediatric patients treated with a recombinant *Escherichia coli (E. coli)*-derived cPMP product (rcPMP) from Colbourne Pharmaceuticals GmbH (Colbourne), [redacted] Published individual case reports suggest that intravenous (IV) administration of rcPMP may restore MoCo-dependent enzyme activities, as evidenced by reduction in the expression of biomarkers of the disease. Highly elevated urinary SSC values observed before initiation of treatment were corrected with rcPMP substitution. rcPMP substitution also resulted in improved neurologic outcomes for patients with MoCD Type A (Veldman et al, 2010; Veldman et al, 2011; Schwahn et al, 2011; Hitzert et al, 2012). The safety data related to these patients from the published literature indicated that the rcPMP infusions were well tolerated. No serious drug-related adverse events (AEs) were reported.

[redacted] This study aims to administer a GMP product, ORGN001, in a controlled setting to eligible patients identified as currently treated with rcPMP [redacted]. The study is designed to evaluate the safety and efficacy of ORGN001 after 6 months of treatment in patients with MoCD Type A who are currently treated with rcPMP. In addition, dose escalation will be performed to determine the starting dose for future studies.

The molecular structures of rcPMP and ORGN001 were compared using multiple spectral techniques [redacted] as well as in vitro efficacy assays, and it has been established that rcPMP and ORGN001 have identical core structures. The identical chemical structures of ORGN001 and rcPMP, together with the nonclinical results obtained with ORGN001 and clinical data obtained in pediatric MoCD Type A patients treated with rcPMP support the use of ORGN001 as a treatment for MoCD Type A. ORGN001 is expected to restore enzymatic activity and correct the metabolic derangement, as evidenced by the reduction in biomarkers of the disease, and thus, prevent the neurologic damage observed in MoCD Type A.

1.3 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 commonly occurs in the neonatal period. Currently, no approved therapy is available 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 that aim to restore MoCo biosynthesis, such as ORGN001, represent one of the most promising therapeutic interventions.

Considering the identical molecular structures of ORGN001 and rcPMP, the clinical results reported with rcPMP, and the nonclinical results with ORGN001, it is anticipated that ORGN001 will benefit patients with MoCD Type A by correcting the metabolic derangement, reconstituting the synthesis of MoCo, and thereby restoring SO enzymatic activity and reducing the levels of the toxic metabolites, sulfite and SSC.

In vitro and preclinical studies have identified that ORGN001 has phototoxic potential. Patients and caregivers are instructed to avoid direct sunlight and to use precautions when exposed to the sun. Protective measures include wearing of sunglasses, a hat, long sleeved shirts, long pants and the use of protective sunscreen.

1.4 Rationale for the Patient Population

The patient population for this study includes the MoCD Type A patients who are currently treated with rcPMP [redacted]. Age at enrollment thereby depends on the age of patients currently treated with rcPMP.

1.5 Rationale for Proposed Dosing

Patients will receive IV infusions of ORGN001 at the same dose as their current dose of rcPMP administered at a rate of 1.5 mL/minute.

ORGN001 drug product has been developed for IV use. Administration via the parenteral route is one of the best options because it provides rapid and consistent onset of action necessary for treatment of MoCD patients. Furthermore, the dose is easy to adapt to body weight, allowing greater dosing accuracy and more flexibility in case an adjustment of the dose is required.

The proposed starting doses are based on the safety and clinical effects reported with rcPMP. The dosing regimen in patients currently treated with rcPMP has been guided by clinical improvement and urine levels of SSC and thiosulfate (Veldman et al, 2010; Veldman et al, 2011; Schwahn et al, 2011; Hitzert et al, 2012). ORGN001 is expected to have similar pharmacodynamic (PD) effects since comparable activities on SO reconstitution and MPT restoration were reported with ORGN001 and rcPMP in vitro (Clinch et al, 2013). [redacted]

Based on the above observations, a dose-escalation scheme will be implemented in this study. Patients will start ORGN001 IV infusions at the same dose level as their current dose of rcPMP. The starting dose will be maintained for 2 months. After the first 2 months of treatment with ORGN001, if the patient's clinical, PK, and safety assessments permit (including the absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 will increase every month [redacted] until either 1) Day 180, 2) the patient reaches a dose that is not tolerated, 3) the patient's exposure exceeds that of the no observed adverse effect level (NOAEL) AUC [redacted], or 4) the patient's exposure following dose escalation is predicted to exceed that of the NOAEL [redacted], whichever comes first. During the

Extension Period, patients who were de-escalated from the final tolerated dose for reasons other than safety or PK considerations may be re-escalated up to their maximally tolerated dose.

1.6 Rationale for the Overall Design

This is a Phase 2, noncomparative, open-label, multicenter, dose-escalation study to assess the safety and efficacy of ORGN001 in pediatric patients with MoCD Type A currently treated with rcPMP.

A placebo-controlled study would not be appropriate due to the severity of the untreated disease and the reported improved outcomes of MoCD Type A newborn infants treated with rcPMP. An active-comparator study is not feasible due to the lack of an approved treatment for MoCD Type A. This study aims to administer a GMP product in a controlled setting to patients currently treated [redacted].

Although this is an open-label study, the design still permits assessment of efficacy since the clinical outcome of untreated patients is well described. It is anticipated that as patients transition to ORGN001, they will have no change in their clinical status, thereby demonstrating comparable efficacy to rcPMP. The safety of ORGN001 will be reviewed continuously on an individual basis, as well as at a group level. A Safety Review Committee (SRC) [redacted] will review all available safety, efficacy, and if available, PK data on an ongoing basis.

1.7 Clinical Studies with ORGN001

Prior to initiation of Study ALXN1101-MCD-201, ORGN001 had not been administered to pediatric patients.

The first-in-human study, ALXN1101-MCD-101, has completed enrollment in adult healthy subjects to investigate the safety, tolerability, and PK of ORGN001. Four cohorts were to receive single doses [redacted], and a fourth dose was to be determined based on PK data from the first 3 cohorts [redacted]. Dose escalation was stopped at the third dose level as the PK exposure exceeded the exposure at the NOAEL [redacted] in the [redacted] adult rat toxicology study. Final results from Study ALXN1101-MCD-101 [redacted] and a review of safety data across all doses did not reveal any safety signals. Data from this study were supportive of the safety of ORGN001 prior to its administration to pediatric patients.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this clinical study is to evaluate the safety of ORGN001 over the first 6 months of treatment.

2.1.2 Secondary Objectives

The secondary objectives of this clinical study are to:

- Characterize the PK of increasing doses of ORGN001
- Evaluate the effect of ORGN001 on urine and blood SSC levels
- Evaluate the effect of ORGN001 on neurologic, motor, and cognitive functions
- Evaluate the effect of ORGN001 on CNS structure
- Evaluate the long-term safety of ORGN001

[redacted]

2.2 Endpoints

The following endpoints will be measured over the first 6 months of treatment and over the entire treatment period:

2.2.1 Safety Endpoints

- Incidence and severity of 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

2.2.2 Efficacy Endpoints

- 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 and Toddler 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

2.2.3 Pharmacokinetic Endpoint

- Pharmacokinetic parameters of ORGN001 including, but not limited to, maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC) and if possible, terminal half-life ($t_{½}$), and dose linearity

[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This Phase 2, multicenter, multinational, open-label, dose-escalation study is designed to evaluate the safety and efficacy of ORGN001 administered to infants and children with MoCD Type A currently treated with rcPMP. [redacted] 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; Figure 1). A patient may be discontinued once ORGN001 is registered and available as a treatment for MoCD Type A in the region where the patient resides or is receiving treatment (in accordance with country-specific requirements).

Screening evaluations will be performed at any time during the Screening Period before the first dose of ORGN001. Enrolled patients will attend at least 2 study visits in order for baseline data to be obtained [redacted]. During the Screening Period, patients will continue to receive daily IV infusions of their current rcPMP treatment.

During the 6-Month Initial Treatment Period, starting on Day 1, patients will begin IV infusions of ORGN001 at the same dose as their current dose of rcPMP, approximately 24 hours after their last treatment with rcPMP. No further treatments with rcPMP will be allowed during the study. Patients [redacted] will continue to receive daily infusions of ORGN001 at home [redacted] and will attend multiple study visits for safety, efficacy, PD and PK assessments through Day 180 [redacted]. After the first 2 months of treatment with ORGN001, if the patient's clinical, PK, and safety assessments permit (including the absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 will increase every month [redacted] based on the patient's clinical response, safety laboratory assessments, and when appropriate, exposure data. After the 6-Month Initial Treatment Period, patients will enter the Extension Period and continue to receive uninterrupted daily dosing of ORGN001 at their final tolerated dose based on the dose escalation. Alternatively, after dose escalation is complete, the patient can be returned to a prior dose based on the patient's clinical status at the discretion of the treating physician after consultation with the SRC. During the Extension Period, patients who were de-escalated from the final tolerated dose for reasons other than safety or PK considerations may be re-escalated up to their maximally tolerated dose. Patients who prematurely discontinue from the study will attend a Safety Follow-up Visit [redacted] and will return to the care of their treating physician.

Every effort should be made to prevent, or if unavoidable, minimize pain as a result of study-related procedures and assessments. Pain will be monitored as per protocol at each study site and treated appropriately. An alternative blood sampling schedule for infants weighing less than 10 kg, for whom less blood volume should be collected, must be used [redacted].

3.2 NUMBER OF PATIENTS

At least 4 patients with MoCD Type A will be enrolled in the study. The actual sample size will depend on the number of eligible patients currently treated with rcPMP [redacted].

3.3 Study Treatment and Dose Escalations

Starting on Day 1 of the 6-Month Initial Treatment Period, patients will discontinue rcPMP treatment and begin IV infusions of ORGN001 at the same dose as their current dose of rcPMP. If the starting dose of ORGN001 is not tolerated or results in exposure exceeding the NOAEL [redacted], the dose will be reduced by 25% (if not tolerated) or to a level that is expected to result in exposure that is below the NOAEL AUC. After the first 2 months of treatment with ORGN001, if the patient's clinical, PK, and safety assessments permit (including the absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 will increase every month [redacted] based on the patient's clinical response, safety laboratory assessments, and when appropriate, exposure data. Dose escalation will occur monthly (with the exception of unscheduled dose adjustments) until either 1) Day 180, 2) the patient reaches a dose that is not tolerated, 3) the patient's exposure exceeds that of the no observed adverse effect level (NOAEL) AUC [redacted], or 4) the patient's exposure following dose escalation is predicted to exceed that of the NOAEL [redacted], whichever comes first, upon recommendation by the SRC/Data Monitoring Committee (DMC) (Sections 3.4 and 16.2).

Approximately 3 days prior to each scheduled dose escalation [redacted], patients will have blood and urine collected for safety laboratory and PD biomarker assessments. These safety laboratory results and clinical assessments from the previous visit [redacted], as well as the PK from the previous dose level, if deemed necessary, will be reviewed by the SRC and DMC; a decision will be made whether to proceed with dose escalation. Patients will attend a Dose-escalation Visit [redacted], where the PI will perform clinical assessments (physical examination, vital signs, neurologic examination, growth parameters, and AEs) prior to administration of ORGN001. If the results of the clinical assessments are acceptable to the PI, ORGN001 will be escalated to a higher dose. If the PI determines that a patient's clinical status has changed, and the dose should not be escalated, the patient's dose will continue at the current dose or at a reduced dose until the SRC and DMC review the patient's status to determine if the dose should be escalated, maintained, stopped, or decreased. [redacted] Additional study visits may be requested at the discretion of the PI. If the patient's dose is escalated, blood will be drawn approximately 1 week later [redacted] for safety laboratory and PD biomarker assessments.

During the Extension Period, patients who were de-escalated from the final tolerated dose for reasons other than safety or PK considerations may be re-escalated up to their maximally tolerated dose. After dose escalation is complete, the patient can be returned to a prior dose based on the patient's clinical status at the discretion of the treating physician after consultation with the SRC.

3.4 SAFETY REVIEW COMMITTEE

In order to monitor patient safety, data will be reviewed daily by the PI or designee during the first 2 weeks following initiation of ORGN001. In particular, the SRC will review blood pressure (BP) data, along with all the other safety data, to determine if continued frequent monitoring is needed. The PI or designee will contact the patient's parent or legal guardian daily at home, as applicable, [redacted] to inquire about the patient's status. The SRC, [redacted] will review all available clinical data after each patient has completed the first 2 weeks of treatment with ORGN001, prior to each patient's scheduled dose escalations in conjunction with the DMC [redacted] and at any other time during the study as requested by the PI or Sponsor. Dose-escalation assessments will be on an individual basis as patients will be enrolled sequentially.

[redacted] Based on the review of the available data, which may include laboratory data, clinical assessments, neuroimaging (if needed), and exposure data, the SRC, in consultation with the DMC, may recommend stopping, increasing, decreasing, or maintaining the dose of ORGN001.

In addition to the scheduled dose escalations, the PI may also convene the SRC for unscheduled dose adjustments based on drug-related AEs and changes in clinical parameters. The SRC chair will also convene the DMC if a dose escalation is being considered or will notify the DMC if the dose is decreased. Blood and urine samples will be collected for PD and PK assessments on the first Day the adjusted dose is administered. Pharmacodynamic and safety laboratory assessments will be repeated [redacted] at the [redacted] Follow-up Visit [redacted].

3.4.1 Criteria to Hold Dose Escalation

The following are examples of possible clinical conditions and potential actions to be taken with respect to study drug administration in a given child or group of children. This list is not comprehensive. Each patient will be assessed individually based on his or her baseline clinical status.

Scenario 1: Any study drug-related SAE that results in death of a single patient

Action: No further dose escalations will take place in any patient; all other patients will maintain their current dose level, pending evaluation.

Scenario 2: One or more study drug-related SAEs in a single patient

Action: The patient's dose is reduced to the previously tolerated dose level. No further dose escalations will take place in that patient, pending evaluation. Dose escalation may be continued in subsequent patients.

Scenario 3: The same severe, study drug-related SAE occurs in 2 different patients

Action: No further dose escalations to the dose level at which the event was noted will take place in any patient, pending evaluation. The dose escalation in subsequent patients will be stopped below the dose where these SAEs were noted.

Scenario 4: PK exposure in a single patient exceeds the NOAEL AUC [redacted].

Action: The patient's dose is reduced to a dose level that results in exposure that is below the NOAEL AUC exposure. Dose escalation will continue in subsequent patients and the PK exposure should not exceed the NOAEL AUC [redacted].

3.4.2 Safety Criteria for Unscheduled Dose Adjustments

Doses may be adjusted based on the occurrence of drug-related AEs and changes in clinical parameters, as assessed by the SRC. The SRC chair will also convene the DMC if a dose escalation is being considered or will notify the DMC if the dose is decreased. If a patient has significant clinical worsening related to ORGN001 dosing, the dose may be decreased based on the clinical status of the patient and, if available, exposure data. If this occurs within the first 2 months, the target dose reduction would be approximately 25% of the starting dose [redacted] or to a level that is expected to result in exposure that is below the NOAEL AUC. If an unscheduled dose adjustment is necessary during Months 2 through 6 of the study, the patient's dose will be reduced to the last tolerated dose. Alternatively, after dose escalation is complete, the patient can be returned to a prior dose based on the patient's clinical status at the discretion of the treating physician after consultation with the SRC.

3.5 Criteria for Site or Study Termination

For reasonable cause, the Investigator, Institutional Review Board (IRB)/Ethics Committee (EC), or Sponsor may terminate the study at a given center, in which case, the care of the patients at the site would be transferred to a different Investigator, or all centers, in which case, patients would return to the care of their treating physician. Conditions that may warrant termination of the study or investigational sites participating in this study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug
- Failure of the Investigator to comply with the approved protocol, pertinent guidelines, and/or regulations
- Submission of knowingly false information from the Investigator to the Sponsor and/or regulatory authorities

The end of the study will be defined as the date of the last patient's last visit.

Figure 1: ALXN1101-MCD-201 Study Design

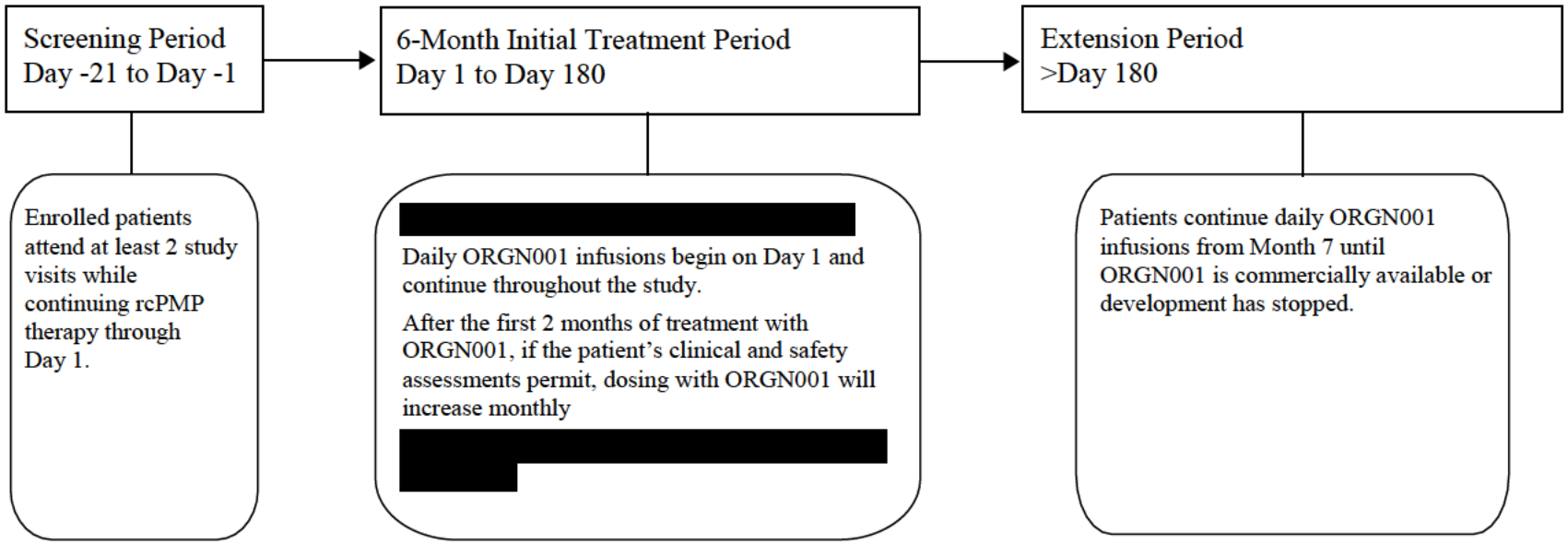


Table 3: Schedule of Assessments (Screening and Month 1 of the 6-Month Initial Treatment Period)

Assessment	**Screening/ Baseline Period[1,2]**	**Month 1 of the 6-Month Initial Treatment Period**
Study Day		
Month		
Visit Window (Days)		
Informed consent		
Eligibility		
Demographic data and onset of disease[5]		
Genotype[7]		
Family history[8]		
Medical history[9]		
Physical examination[25]		
Vital signs[12,25]		
Additional BP measurements		
Serum chemistry and hematology[13, 25]		
Coagulation[14]		
Urinalysis[15, 25]		
Growth parameters[16]		
Feeding pattern[17]		
Neurologic examination[25]		
GMFCS		
Bayley-III (age-appropriate test)[19]		
WPPSI[20]		
Record seizure diary data[21, 25]		
Neuroimaging[22]		
EEG[23]		
PD sampling, urine[24,25]		

Assessment	Screening/ Baseline Period[1,2]	Month 1 of the 6-Month Initial Treatment Period
Study Day	[redacted]	
Month		
Visit Window (Days)		
PD sampling, blood[25,28]		
PK sampling[25]		
ORGN001 infusion[31]		
Assess concomitant meds/ procedures[25,32]		
Assess AEs[25]		

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. [redacted]

[1] No study procedures may be performed prior to obtaining informed consent. An alternative blood sampling schedule for infants weighing less than 10 kg, for whom less blood volume should be collected, must be used as [redacted].

[2] Patients continue daily rcPMP infusions on Days -21 through -1. The last rcPMP infusion will be administered approximately 24 hours (±3 hours) prior to the first dose of ORGN001. No further infusions of rcPMP will be permitted after Day -1.

[3] Enrolled patients must attend at least 2 separate study visits during Days -21 through -1 in order for baseline data to be obtained.

[redacted]

[5] Record patient's date of birth, gender, gestational age, race and ethnicity. If available, document information on parity, any complications during pregnancy, delivery type, Apgar scores, placental condition, and history of in utero seizures. Dates of onset of signs and symptoms suggestive of MoCD will be recorded, as available.

[6] After informed consent has been obtained, assessment may be performed at any time from Days -21 to -1, inclusive.

[7] Obtain documentation of previous MoCD Type A genetic confirmation. If documentation is not available, collect a 1.0 mL venous blood sample for genotyping.

[8] Record parental consanguinity, parental genotype of MoCD (if known), and whether the patient has any other siblings (living or deceased) with suspected or confirmed MoCD.

[9] Request documentation of previous vision/hearing assessments.

[10] Record ascites and hepatic encephalopathy scores to calculate Child-Pugh score.

[11] Performed within 24 hours prior to infusion.

[12] Include heart rate, respiratory rate, BP, and temperature.

[13] Include complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, total serum albumin, and serum osmolality.

[14] Include international normalized ratio and prothrombin time.
[15] Obtain a urine sample for urinalysis. Include specific gravity, pH, glucose, protein, blood and ketones (by dipstick and microscopic examination), and urine protein to creatinine ratio. Urinalysis is to be conducted at scheduled assessments unless clinically indicated otherwise.
[16] Record body length, body weight, and head circumference.
[17] Record if patient is able to feed orally or feeds through a nasogastric or gastronomy feeding tube.
[18] Performed within 2 hours prior to infusion.
[19] Bayley-III to be completed for patients less than 3 years of age. However, for patients over 3 years of age with severe developmental delay, the Bayley-III may be more appropriate than the WPPSI and may therefore be administered instead. Scales administered in this study will include the Cognitive Scale and the Motor Scale. The Language Scale will be also administered in English-speaking countries to patients who are native English speakers.
[20] WPPSI to be completed only for patients 3 years of age or older. For patients with severe developmental delay, the WPPSI may not be an appropriate assessment, and therefore, the Bayley-III may be administered instead.
[21] At the first study visit in the Screening Period, the frequency of seizures over the prior month will be collected by recall and a seizure diary will be dispensed. The parent/legal guardian is to enter seizure data (incidence) in the seizure diary each Day for the entire duration of the study. Collect seizure diary at all visits, record seizure data in the CRF/eCRF, and dispense a new diary to the parent/legal guardian.
[22] May provide a previous MRI assessment if performed within 6 months prior to enrollment and the patient has remained stable. Neuroimaging will be conducted [redacted] if clinical condition allows (additional scans may be requested as needed). Magnetic resonance imaging is the preferred imaging modality, but a computed tomography scan is acceptable if a patient's clinical status does not allow for an MRI. Copies of the scan data will be collected. [redacted]
[23] May provide previous assessment if performed within 6 months prior to enrollment and the patient's seizure frequency has not changed significantly since that study. Perform standard EEG [redacted]. Additional EEGs may be performed at the discretion of the treating physician.
[24] Collect a urine sample [redacted] for evaluation of SSC, [redacted]
[25] If an unscheduled dose adjustment is recommended by the SRC, or after dose escalation is complete and the patient is returned to a prior dose based on the patient's clinical status at the discretion of the treating physician after consultation with the SRC, see Table 5 for additional assessments.
[26] Two samples must be collected [redacted] 2 separate visits (i.e., 1 collection at each visit) during the Screening Period.
[27] Sample to be collected prior to first infusion. If a baseline sample was collected on Day -1, the Day 1 sample should be collected only after at least 24 hours have elapsed.
[28] Collect a venous blood sample [redacted] for PD analysis. If collected on the same Day as neurocognitive assessments, collect blood after assessments.
[29] Collect venous blood samples [redacted] preinfusion, EOI, and 4 hours post-EOI (±5 minutes for all time points).
[30] Collect venous blood samples [redacted] at EOI, 0.5, 1, 2, 3, and 5 hours post-EOI (±5 minutes for all time points).
[31] Daily IV infusions of ORGN001 (24 hours ± 3 hours apart) occur either while in-patient or at home.
[32] Changes in seizure medications, including the reason for the change, will be recorded.
[33] Additional BP measurements are to be conducted prior to the infusion and at 30, 60, 90, and 120 minutes post-EOI, followed by hourly assessments until 6 hours post-EOI, then every 6 hours until the next dose.
[34] Additional BP measurements are to be conducted prior to the infusion and hourly post EOI for 6 hours, then every 6 hours until the next dose. The SRC will review the blood pressure data along with all the other safety data to determine if continued frequent monitoring is needed.
[35] An optional blood sample and urine sample will be collected at 24 hours after the EOI for PK and PD assessments.
Abbreviations: AEs = adverse events; Bayley-III = Bayley Scales of Infant and Toddler Development-Third Edition; BP = blood pressure; CRF = case report form; EEG = electroencephalogram; eCRF = electronic case report form; EOI = end of infusion; GMFCS = Gross Motor Function Classification System; meds =

medications; MoCD = molybdenum cofactor deficiency; MRI = magnetic resonance imaging; PD = pharmacodynamics; PI = principal investigator; PK = pharmacokinetics; rcPMP = recombinant *E. coli*-derived cPMP; SRC = Safety Review Committee; SSC = S-sulfocysteine; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

Table 4: Schedule of Assessments (Months 2 through 6 of the 6-Month Initial Treatment Period)

Assessment	Months 2 through 6 of the 6-Month Initial Treatment Period												
Study Day	[redacted]												
Month													
Visit Window (Days)													
Physical examination[15]													
Vital signs[3, 15]													
Serum chemistry and hematology[4, 15]													
Coagulation[5]													
Urinalysis[6, 15]													
Growth parameters[7]													
Feeding pattern[8]													
Neurologic examination[15]													
GMFCS													
Bayley-III (age-appropriate test)[9]													
WPPSI[10]													
Record seizure diary data[11, 15]													
Neuroimaging[12]													
EEG[13]													
PD sampling, urine[14,15]													
PD sampling, blood[15,16]													
[redacted]													
PK sampling[15]													
ORGN001 infusion	X[20]	X[21]	X[22]	X[20]	X[21]	X[22]	X[20]	X[21]	X[22]	X[20]	X[21]	X[22]	X[21]
Assess concomitant meds/ procedures[15, 23]	[redacted]												

Assess AEs[15]	[redacted]

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. [redacted]

[1] Assessments at this visit must occur prior to the subsequent visit [redacted], but do not require an in-clinic visit for blood or urine collection. If the assessments are completed in-clinic, concomitant medications/procedures and AEs should be assessed.

[2] Record ascites and hepatic encephalopathy scores to calculate Child-Pugh score.

[3] Include heart rate, respiratory rate, blood pressure, and temperature.

[4] Include complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, total serum albumin, and serum osmolality.

[5] Include international normalized ratio and prothrombin time.

[6] Obtain a urine sample for urinalysis. Include specific gravity, pH, glucose, protein, blood and ketones (by dipstick and microscopic examination), and urine protein to creatinine ratio. Urinalysis is to be conducted [redacted] unless clinically indicated otherwise.

[7] Record body length, body weight, and head circumference.

[8] Record if patient is able to feed orally or feeds through a nasogastric or gastronomy feeding tube.

[9] Bayley-III to be completed for patients less than 3 years of age. However, for patients over 3 years of age with severe developmental delay, the Bayley-III may be more appropriate than the WPPSI and may therefore be administered instead. Scales administered in this study will include the Cognitive Scale and the Motor Scale. The Language Scale will be also administered in English-speaking countries to patients who are native English speakers.

[10] WPPSI to be completed only for patients 3 years of age or older. For patients with severe developmental delay, the WPPSI may not be an appropriate assessment, and therefore, the Bayley-III may be administered instead.

[11] The parent/legal guardian is to enter seizure data (incidence) in the seizure diary each Day for the entire duration of the study. Collect seizure diary at all visits, record seizure data in the CRF/eCRF, and dispense a new diary to the parent/legal guardian.

[12] Neuroimaging will be conducted [redacted] if clinical condition allows (additional scans may be requested as needed). Magnetic resonance imaging is the preferred imaging modality, but a computed tomography scan is acceptable if a patient's clinical status does not allow for an MRI. Copies of the scan data will be collected. [redacted]

[13] Perform standard EEG [redacted]. Additional EEGs may be performed at the discretion of the treating physician.

[14] Collect a urine sample [redacted] for evaluation of SSC, [redacted]

[15] If an unscheduled dose adjustment is recommended by the SRC, or after dose escalation is complete and the patient is returned to a prior dose based on the patient's clinical status at the discretion of the treating physician after consultation with the SRC [redacted].

[16] Collect a venous blood sample [redacted] for PD analysis. If collected on the same Day as neurocognitive assessments, collect blood after assessments. [redacted]

[18] Collect capillary blood samples [redacted] at the EOI and 4 hours post-EOI prior to collection of the corresponding venous blood samples. Collect venous blood samples [redacted] within 5 minutes of the corresponding capillary blood samples, if possible, at the EOI and 4 hours post-EOI.

[19] Collect venous blood samples [redacted] at the EOI (±5 minutes) and 4 hours post-EOI (±5 minutes).

[20] Daily IV infusion of ORGN001 (24 hours ± 3 hours apart) occurs at home.

[21] Daily IV infusion of ORGN001 (24 hours ± 3 hours apart) occurs while in-clinic.

[22] Daily IV infusion of ORGN001 (24 hours ± 3 hours apart) can occur at home or while in-clinic
[23] Changes in seizure medications, including the reason for the change, will be recorded.
[24] Assessed only if the patient is seen in-clinic. An in-clinic visit is not required for blood and urine collection on this day.
Abbreviations: AEs = adverse events; Bayley-III = Bayley Scales of Infant and Toddler Development-Third Edition; CRF = case report form; EEG = electroencephalogram; eCRF = electronic case report form; EOI = end of infusion; GMFCS = Gross Motor Function Classification System; meds = medications; MRI = magnetic resonance imaging; PD = pharmacodynamics; PK = pharmacokinetics; rcPMP = recombinant E. coli-derived cPMP; SRC = Safety Review Committee; SSC = S-sulfocysteine; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

Table 5: Schedule of Assessments for an Unscheduled Dose Adjustment

Assessment[1]	Specific Time	First Day Adjusted Dose is Administered	[redacted]	Follow-Up Visit[2]
Physical examination[3]	Any time during study visit	[redacted]		
Vital signs	Any time during study visit			
Neurologic examination	Prior to the first blood draw			
PD sampling, urine[4]	Any time during study visit			
PD sampling, blood[5]	3 to 4 hours after the EOI			
PK sampling[6]	EOI			
PK sampling[6]	3 to 4 hours after the EOI			
Serum chemistry, hematology[7]	Any time during study visit			
Urinalysis[8]	Any time during study visit			
Record seizure diary data[9]	Any time during study visit			
ORGN001 infusion	Any time during study visit			
Assess concomitant meds/procedures[10]	Any time during study visit			
Assess AEs	End of the study visit			

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented and the Investigator should provide justification for the deviation. [redacted]

[1] Assessments performed following an unscheduled dose adjustment recommended by the SRC or after dose escalation is complete and the patient is returned to a prior dose; based on the patient's clinical status at the discretion of the treating physician after consultation with the SRC.

[2] Patients return to the clinic [redacted] after [redacted] the adjusted dose is administered. [redacted] If the [redacted] Follow-up Visit falls on a Day when developmental assessments (eg, Bayley-III) were scheduled to be assessed, the study visit that includes the developmental assessments will be rescheduled for the following week.

[3] If either visit occurs on a Day when the Child-Pugh score was scheduled to be assessed [redacted], record ascites and hepatic encephalopathy scores to calculate the Child-Pugh score.

[4] Collect a urine sample [redacted] for evaluation of SSC, [redacted]

[5] Collect a venous blood sample [redacted] for PD analysis.

[6] Collect venous blood samples [redacted] for analysis of PK parameters.

[7] Include complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, serum osmolality, and total serum albumin. If the [redacted] follow up visit coincides with a scheduled coagulation assessment, the blood sample should be analyzed for prothrombin time and the international normalized ratio will be calculated.

[8] Include specific gravity, pH, glucose, protein, blood and ketones (by dipstick and microscopic examination), and urine protein to creatinine ratio.

[9] Collect the seizure diary, record seizure data in the CRF/eCRF, and dispense a new diary to the parent/legal guardian.

[10] Changes in seizure medications, including the reason for the change, will be recorded.

Abbreviations: AEs = adverse events; CRF = case report form; eCRF = electronic case report form; EOI = end of infusion; meds = medications; PD = pharmacodynamics; PK = pharmacokinetics; SRC = Safety Review Committee.

Table 6: Schedule of Assessments (Extension Period and Safety Follow-Up)

Assessment	Extension Period[15]	Safety Follow- Up
Month	[redacted]	
Visit Window (Days)		
Physical examination		
Vital signs		
Serum chemistry and hematology[1]		
Urinalysis[2]		
Growth parameters[3]		
Feeding pattern[4]		
Neurologic examination		
GMFCS		
Bayley-III (age-appropriate test)		
WPPSI[5]		
Record seizure diary data[6]		
Neuroimaging[7]		
EEG[9]		
PD sampling, urine[10]		
PD sampling, predose blood, one-time		
PD sampling, blood[11]		
PK sampling, blood[12]		
ORGN001 infusion[13]	Daily	
Assess concomitant meds/ procedures[14]	[redacted]	
Assess AEs		

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented and the Investigator should provide justification for the deviation.

[redacted]

[1] Include complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, total serum albumin, and serum osmolality.

[2] Obtain a urine sample for urinalysis. Include specific gravity, pH, glucose, protein, blood and ketones (by dipstick and microscopic examination), and urine protein to creatinine ratio. Urinalysis to be conducted [redacted] unless clinically indicated otherwise.

[3] Record body length, body weight and head circumference.

[4] Record if patient is able to feed orally or feeds through a nasogastric or gastronomy feeding tube.

[5] WPPSI to be completed only for patients 3 years of age or older.

[6] Collect seizure diary at all visits, record seizure data in the CRF/eCRF, and dispense a new diary to the parent/legal guardian.

[7] Neuroimaging will be conducted per schedule if clinical condition allows (additional scans may be requested as needed). Magnetic resonance imaging is the preferred imaging modality, but a computed tomography scan is acceptable if a patient's clinical status does not allow for an MRI. Copies of the scan data will be collected. [redacted]

[8] Neuroimaging is optional if the patient's clinical status has not changed since neuroimaging at Month 6.

[9] Perform standard EEG with patient [redacted]. EEG is only performed if clinically indicated. Additional EEGs may be performed at the discretion of the treating physician.

[10] Collect a urine sample [redacted] for evaluation of SSC, [redacted] uric acid and urinary creatinine.

[11] Collect venous blood samples [redacted] after EOI for SSC, [redacted] biomarker analysis. [redacted]

[12] [redacted] PK samples will be collected once [redacted] during the Extension Period.

[13] Daily IV infusions of ORGN001 (24 hours ± 3 hours apart) occur either while in-the hospital or at home.

[14] Changes in seizure medications, including the reason for the change, will be recorded.

[15] A patient may be discontinued once ORGN001 is registered and available as a treatment for MoCD Type A deficiency in the region where the patient resides or is receiving treatment (in accordance with country-specific requirements). The end of the study will be defined as the last patient's last visit.

[redacted]

[redacted] Visit assessments will occur until the patient is discontinued from the study or until ORGN001 is commercially available or development has stopped.

[redacted]

Abbreviations: AEs=adverse events; Bayley-III=Bayley Scales of Infant and Toddler Development-Third Edition; CRF: case report form; EEG=electroencephalogram; eCRF: electronic case report form; GMFCS=Gross Motor Function Classification System; meds=medications; MRI=magnetic resonance imaging; PD=pharmacodynamics; SSC= S-sulfocysteine; WPPSI=Wechsler Preschool and Primary Scale of Intelligence.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Patient Recruitment and Consent

[redacted]

Physicians who have been treating patients [redacted] with rcPMP will be contacted by a representative of the Sponsor or designee to inform them about the commencement of this study. Treating physicians will be responsible for discussing the therapeutic options for the patient with his/her parent or legal guardian.

Should (a) parent or legal guardian choose to enroll their child in this study, they will have to provide informed consent. Before recruitment and enrollment, the parent or legal guardian of each prospective patient will be given a full explanation of the study and be allowed to read the approved Informed Consent Form (ICF). After a comprehensive description of the protocol, review of informed consent, and all questions have been answered, the patient's parent or legal guardian will have the opportunity to decide if he/she wants the child to participate in the study. Once the Investigator is assured that the patient's parent or legal guardian understands the implications of participating in the study, written informed consent must be obtained. The site will keep the original ICF and provide a copy to the parent/legal guardian. After the ICF is signed, the patient will be assessed for eligibility for inclusion into the study. Informed consent must be obtained prior to performing any study-related procedures and can be obtained before the Screening Visit.

4.2 Patient Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in the study:

1. Male or female patients with a genetically confirmed diagnosis of MoCD Type A (MOCS1 mutation)
2. Currently treated with rcPMP infusions
3. Parent or legal guardian must have signed the ICF prior to any study procedures

4.3 Patient Exclusion Criteria

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

4.4 Patient Withdrawal Criteria

A patient's parent or legal guardian has the right to withdraw a child from the study at any time for any reason without prejudice to their medical care. Patients who withdraw from the study will return to the care of their treating physician.

Patients may be withdrawn from the study, with or without their consent, for reasons including, but not limited to, the following:

- Patient (and/or parent or legal guardian) request
- Patient and/or parent or legal guardian is unwilling or unable to comply with the protocol
- Intolerable AE or other medical reason, at the discretion of the Investigator and/or Medical Monitor in consultation with the SRC, as appropriate

All patients who discontinue or are withdrawn from the study will be encouraged to complete the Safety Follow-up Visit [redacted]. The reasons for premature study withdrawal must be recorded in the patient's case report form (CRF)/electronic case report form (eCRF) and in the source records.

For patients who are prematurely withdrawn from the study due to clinical safety concerns (eg, intolerable AEs), the Investigator must immediately notify the Medical Monitor. In these patients, AEs leading to premature withdrawal must be followed until resolution or the patient is determined to be medically stable, in the opinion of the Investigator. Patients who withdraw from the study will not be replaced.

5 TREATMENT OF PATIENTS

5.1 Description of Study Drug

ORGN001, a synthetic form of cPMP, is an investigational drug. A detailed description can be found in Table 7.

Table 7: ORGN001 Description

	Study Drug
Product Name	ORGN001 (formerly ALXN1101)
Dosage Form	Powder for solution for infusion
Strength	[redacted]
Route of Administration	IV use
Physical Description	Sterile, [redacted] white to slightly yellow lyophilized powder
Manufacturer	[redacted]

5.2 Prior and Concomitant Medications and Procedures

Prior medications (any drug or substance taken by the patient within 28 days prior to the time the patient's parent or legal guardian signs the informed consent until the first dose of study drug) and concomitant medications (any drug or substance taken by the patient after the first dose of study drug until completion of the last study visit) will be recorded on the patient's CRF/eCRF. Prior procedures (any therapeutic intervention [eg, surgery/biopsy, physical therapy] performed within 28 days prior to the time the patient's parent or legal guardian signs the informed consent until the first dose of study drug) and concomitant procedures (any therapeutic intervention [eg, surgery/biopsy, physical therapy] performed after the first dose of study drug until completion of the last study visit) will be recorded on the patient's CRF/eCRF. If possible, elective surgical procedures should not be performed during the 6-Month Initial Treatment Period.

The use of concomitant medication or concomitant procedure as defined above must be recorded on the patient's CRF/eCRF, according to instructions for CRF/eCRF completion. Changes in a patient's seizure medications, including the reason for the change, will be recorded. Adverse events related to administration of these therapies or procedures must be documented on the appropriate CRF/eCRF.

5.3 Treatment Compliance

The Investigator or designee must ensure that the parent or legal guardian of all study participants are adequately informed of the study drug regimen required for compliance with the study protocol. Daily infusions of ORGN001 at home will be administered by the patient's parent or legal guardian with the support of at-home infusion support services. Patient compliance with the study drug regimen will be continually monitored throughout the study by means of review of study drug administration records and study drug accountability. Study drug accountability (including accounting of study drug returns) will be reviewed with the patient's parent or legal guardian at each study visit.

[redacted] Missed treatments must be clearly documented in the patient's study records and recorded in the CRF/eCRF. Additionally, these must be documented as protocol deviations.

6 STUDY DRUG MATERIALS AND MANAGEMENT

6.1 Study Drug

ORGN001 is supplied as a sterile, [redacted] white to slightly yellow lyophilized powder, [redacted]. The drug product is designed to be reconstituted using sterile Water for Injection as the diluent. [redacted]

6.2 Study Drug Packaging and Labeling

ORGN001 is supplied in a single-use, stoppered, [redacted] glass vial for reconstitution.

[redacted]

6.3 Study Drug Storage

ORGN001 vials must be stored frozen at -10°C to -25°C protected from light. Following reconstitution, ORGN001 should be administered within 4 hours. Reconstituted ORGN001 may be stored at 2°C to 8°C or room temperature prior to administration. If stored at 2°C to 8°C, reconstituted ORGN001 should be allowed to come to room temperature before infusion.

Reconstituted ORGN001 must not be heated (eg, by using a microwave or other heat source) other than by ambient air temperature.

6.4 Study Drug Preparation

Dose adjustments to account for changes in body weight (rounded up to the nearest kilogram) will be assessed [redacted] at each scheduled study visit [redacted].

Reconstitute ORGN001 with [redacted] sterile Water for Injection [redacted].

[redacted]

6.5 Study Drug Administration

Starting on Day 1, patients will begin daily IV infusions of ORGN001 at the same dose as their current dose of rcPMP, approximately 24 hours (±3 hours) after their last treatment with rcPMP. [redacted] The parent or legal guardian will be trained on proper storage, preparation, and administration of study drug for dosing at home [redacted]. All doses will be administered by IV infusion at a rate of 1.5 mL/minute. [redacted]

7 STUDY DRUG ACCOUNTABILITY

Each investigational study site must maintain accurate records demonstrating dates and amount of study drug received, to whom dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed.

Unless otherwise notified, all vials both used and unused, must be saved for study drug accountability. At the end of the study, a final reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to the Sponsor.

A written explanation will be provided for any discrepancies. After reconciliation, the Investigator must destroy or return all unused vials of study drug as instructed by the Sponsor.

If any study drug supplies are to be destroyed at the site, the Investigator must obtain prior approval by the Sponsor. The Investigator must notify the Sponsor, in writing, of the method of destruction, the date of destruction, and the location of destruction.

Destruction of unused vials of study drug by the Investigator must be in compliance with federal, state, country, and local regulations.

7.1 Study Drug Handling and Disposal

ORGN001 should be handled with care. Aseptic technique should be used for dose preparation.

In the event of a spill, use universal precautions for clean-up. Dispose of any spilled material in compliance with federal, state, and/or local regulations.

[redacted]

8 SCREENING ASSESSMENTS

Screening assessments will be performed [redacted].

8.1 Informed Consent

No study procedures, including screening assessments, may be performed prior to obtaining informed consent. Screening assessments may be performed at any time between Day -21 to -1.

8.2 Demographic Data and Onset of Disease

A patient's date of birth, gender, gestational age, race and ethnicity will be recorded at Screening. If available, information on parity, any complications during pregnancy, delivery type, Apgar scores, placental condition, and history of *in utero* seizures will be recorded. Date of onset of signs and symptoms suggestive of MoCD will be recorded, as available.

8.3 Medical History, Family History, and Genotype

A review of the patient's medical history will be conducted at Screening. Documentation of previous MoCD Type A genetic confirmation will be obtained. The degree of parental consanguinity and parental genotypes, if known, should be recorded. If applicable, siblings (living or deceased) with suspected or confirmed MoCD should be recorded.

Documentation from previous vision and hearing assessments will be obtained.

9 EFFICACY ASSESSMENTS

[redacted]

9.1 Neurologic Examinations

Neurologic examinations will be performed [redacted]. The Day 1 assessment must be performed within 2 hours prior to the first infusion. Neurologic examinations are also performed if patients have unscheduled dose adjustments [redacted]. Neurologic examination includes, but is not limited to, assessment of mental status, cranial nerves, motor strength and tone, sensory examination, deep tendon reflexes and primitive reflexes, if present.

9.2 Bayley Scales of Infant and Toddler Development

The Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) will be administered [redacted] to assess changes in gross motor, fine motor, language, and cognitive development. The Bayley-III will be administered to children less than 3 years of age. Additionally, for patients over 3 years of age with severe developmental delay, the Bayley-III may be more appropriate than the WPPSI and may therefore be administered instead.

The Bayley-III is a standardized and norm-referenced instrument that assesses changes in gross motor, fine motor, language, and cognitive development. It is administered in infants and children 1 month to 42 months of age.

The Bayley-III consists of a core battery of the following 5 scales, 3 of which are administered by a trained qualified professional with child interaction: the Cognitive Scale, the Language Scale (including the Receptive Communication and Expressive Communication subtests), and the Motor Scale (including the Fine Motor and Gross Motor subtests). The Social-Emotional Scale and Adaptive Behavior Scale together form the Social-Emotional and Adaptive Behavior Questionnaire, which is completed by the parent, legal guardian, or primary caregiver. This caregiver-administered portion of the Bayley-III will not be administered as part of this study. The Bayley-III assessments must be performed in the order specified in the Bayley-III Manual.

The Language Scale will be administered only to native English speakers in English-speaking countries.

From raw scores, scaled scores, developmental age equivalents, and growth scores can be calculated for the Cognitive, Receptive and Expressive Communication, Fine Motor, and Gross Motor subtests. Scaled scores also can be used to calculate the Cognitive, Language, and Motor composite scores, percentile ranks, and confidence intervals.

A qualified professional will administer the Bayley-III and determine the appropriateness of each assessment.

9.3 THE GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM

Gross motor function using the GMFCS will be assessed [redacted].

The GMFCS is a 5-level classification system that describes the gross motor function of children and youth (up to 18 years of age) on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility for children with impaired motor skills.

Distinctions between levels are based on functional abilities, the need for assistive technology, including hand-held mobility devices (walkers, crutches, or canes) or wheeled mobility, and to a much lesser extent, quality of movement.

Children who have motor functions similar to those classified in "Level I" can generally walk without restrictions but tend to be limited in some of the more advanced motor skills. Children

whose motor function has been classified at "Level V" are generally very limited in their ability to move themselves around even with the use of assistive technology.

The Investigator or designee will assess the patient according to the levels of the GMFCS.

9.4 Wechsler Preschool and Primary Scale of Intelligence

The Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI) will be administered to children 3 years of age or older by a neurocognitive expert [redacted]. For patients with severe developmental delay, the WPPSI may not be an appropriate assessment, and therefore, the Bayley-III may be administered instead.

The WPPSI is an intelligence measure designed for children ages 2 years, 6 months to 7 years, 7 months. The WPPSI consists of 15 subtests from which the composite scores are derived.

9.5 Seizure Diary

At Screening, the patient's parent or legal guardian will be asked to recall the frequency of seizures over the prior month and the patient's history of seizure medication, including the start and stop dates, dose, and frequency of each seizure medication. The patient's parent or legal guardian will be given a diary to be used to record data regarding the frequency of seizures and any changes in seizure medication for the entire duration of the study.

The Investigator or designee will collect the diary at study visits [redacted], record diary data entered by the parent or legal guardian into the CRF/eCRF, and issue a new diary. The diary will be reviewed to identify any medications that were administered for a flurry of seizures or a prolonged seizure and if any changes in seizure medications were made since the last study visit.

9.6 Neuroimaging

Magnetic resonance imaging (MRI) scans are the preferred imaging modality and should be performed [redacted] if the patient's clinical condition allows. An MRI at Month 12 and beyond is optional if the patient's clinical status has not changed since the MRI at Month 6. Additional scans may be requested as needed. A previous MRI scan may be provided in lieu of a scan during the Screening Period if the previous scan was performed within 6 months prior to enrollment and the patient has remained stable.

[redacted]

If, in the opinion of the PI, MRI is not possible due to the patient's clinical condition, a computed tomography (CT) scan without contrast should be performed.

9.7 Growth Parameters

Body weight, body length, and head circumference will be measured [redacted].

9.8 Feeding Pattern Assessment

Record if patient is able to feed orally or feeds through a nasogastric or [redacted] feeding tube [redacted] or if there is a change in feeding pattern at any time.

10 PHARMACODYNAMIC ASSESSMENTS

Pharmacodynamic biomarker assessments will be performed [redacted]. An alternative blood sampling schedule for infants weighing less than 10 kg, for whom less blood volume should be collected, must be used [redacted].

Urine samples will be collected [redacted]. An additional optional urine sample may be collected [redacted] for PD assessment at the visit on Day 1. [redacted]

Venous blood samples will be collected [redacted]. In addition, a PD blood sample will be collected prior to the ORGN001 infusion at one time between Month 7 and the last month of the Extension Period. [redacted]

Samples will be evaluated for biomarkers of the MoCD pathway, which may include, but are not limited to, SSC, [redacted] levels. [redacted]

During the Screening Period (Day -21 to Day -1), both urine and blood samples must be collected [redacted], in order to calculate baseline levels. On Day 1, a urine sample and a blood sample are to be collected prior to the first infusion. [redacted]

Following recommendation by the SRC for an unscheduled dose adjustment during the 6-Month Initial Treatment Period, or after dose escalation is complete and the patient is returned to a prior dose, additional blood and urine samples will be collected to evaluate the changes in SSC, [redacted], uric acid, urinary creatinine, [redacted]:

- On the first Day the adjusted dose is administered, as well as [redacted] at the [redacted] Follow-up Visit, the patient will be administered study drug in-clinic, and a blood sample will be collected at 3 to 4 hours after the EOI. A urine sample will be collected at any time during the study visit.
- If either visit coincides with a previously scheduled PD sample collection, only 1 PD blood sample [redacted] and 1 PD urine sample [redacted] should be collected at that visit.

Under no circumstance will the total blood volume obtained exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. [redacted]

[redacted]

11 PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic assessments will be performed [redacted]. An alternative blood sampling schedule for infants weighing less than 10 kg, for whom less blood volume should be collected, must be used [redacted].

Blood samples will be collected for assessment of PK parameters (C_{max}, t_{max}, AUC, and $t_{1/2}$) if the patient's clinical condition allows. [redacted]. Dosing date, time, amount, and infusion time of the 3 previous doses (except for Day 1) prior to a PK sample collection will be recorded in the CRF/eCRF.

Table 8: Pharmacokinetic Sampling Schedule

	Study Visit
Blood Sample Collection Time point	[redacted]
Preinfusion[2]	
EOI[3]	
0.5 hour after the EOI[3]	
1 hour after the EOI[3]	
2 hours after the EOI[3]	
3 hours after the EOI[3,4]	
4 hours after the EOI[3,4]	
5 hours after the EOI[3]	
24 hours after the EOI[5]	

[1] Two venous blood samples will be collected for the EOI and 4 hours post-EOI time points at any one visit during the Extension Period.

[2] Venous blood samples collected within 60 minutes prior to start of infusion.

[3] Venous blood sample must be collected within a window of ±5 minutes. (Note the sampling at the EOI time point should not occur prior to the completion of the infusion.)

[4] Capillary blood samples [redacted] collected at EOI and post-EOI prior to the corresponding venous blood sample collection. [redacted]

[5] An optional venous blood sample may be collected 24 hours after the EOI.

Abbreviation: EOI = end of infusion.

Following recommendation by the SRC for an unscheduled dose adjustment during the 6-Month Initial Treatment Period, or after dose escalation is complete and the patient is returned to a prior dose, blood samples will be collected for assessment of PK parameters as follows [redacted]:

- On the first Day the adjusted dose is administered, the patient will be administered study drug in-clinic, and a blood sample will be collected at the EOI (±5 minutes) and at 3 to 4 hours after the EOI. The time of the PK sample collection, the dose administered and the start and stop time of IV infusion are to be recorded in the CRF/eCRF.
- If the visit coincides with a previously scheduled PK sample collection, the previously scheduled PK sample collection for that Day will be cancelled with the exception of capillary blood samples on Day 60. Capillary blood samples on Day 60 will be collected 5 min prior to venous blood samples.

Under no circumstance will the total blood volume obtained exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented and the Investigator should provide justification for the deviation. [redacted]

12 SAFETY ASSESSMENTS

Safety assessments will be performed [redacted]. If multiple assessments of a single parameter are performed within a time period (i.e., multiple measurements of laboratory assessments on Day 1), further instruction will be provided in the CRF/eCRF manual as to which data to collect.

12.1 Vital Signs

Vital signs will be taken [redacted]. On Day 1, vital signs are to be taken within 24 hours prior to infusion. Vital signs will include heart rate, respiratory rate, BP, and temperature.

[redacted]

12.1.1 Additional Blood Pressure Measurements

[redacted]

All additional BP measurements [redacted] must be recorded in the CRF/eCRF [redacted].

12.2 Physical Examination

A complete physical examination [redacted] will be performed [redacted]. On Day 1, the physical examination is to be performed within 24 hours prior to infusion.

Ascites and hepatic encephalopathy scores will be recorded [redacted] and the Child-Pugh score will be calculated.

Assign a score of 1, 2 or 3 for each of the following categories according to the criteria in Table 9. The total of the scores determines the Child-Pugh score as Grade A (5--6), Grade B (7-9), or Grade C (10-15).

Table 9: Criteria for Child-Pugh Classification

Clinical or Biochemical Measurements	Points Scored for Increasing Abnormality			Enter Assigned Score
	1	2	3	
Hepatic encephalopathy (grade)	Absent	1 and 2	3 and 4	
Ascites	Absent	Mild	Moderate	
Total bilirubin (mg/dl)	<2.0	2.0-3.0	>3.0	
Serum albumin (g/dl)	>3.5	2.8-3.5	<2.8	
Prothrombin time INR	<1.7	1.7-2.3	>2.3	
			Total Score	

Abbreviation: INR=International normalized ratio

12.3 Laboratory Assessments

Blood samples will be collected for analysis of hematology, serum chemistry and coagulation parameters. Urine samples will be collected for urinalysis. [redacted]. The PI or delegate will review, sign and date laboratory reports as well as indicating if abnormal results are clinically significant or not clinically significant.

Abnormal results will be followed up at the discretion of the Investigator. An alternative blood sampling schedule for infants weighing less than 10 kg, for whom less blood volume should be collected, must be used [redacted].

Following recommendation by the SRC for an unscheduled dose adjustment during the 6-Month Initial Treatment Period, or after dose escalation is complete and the patient is returned to a prior dose blood and urine samples will be collected for assessment of hematology, serum chemistry, and urinalysis as follows [redacted]:

- Seven days after the adjusted dose is administered at the [redacted] Follow-up Visit, the study drug will be administered in-clinic. A blood and a urine sample will be collected at any time during this study visit.
- [redacted]
- [redacted]

Under no circumstance will the total blood volume obtained exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented and the Investigator should provide justification for the deviation. [redacted]

12.3.1 Hematology

Blood samples will be collected [redacted]. On Day 1, the blood sample is to be taken within 24 hours prior to infusion. Samples will be analyzed for a complete blood count which includes: platelet count, red blood cell (RBC) count, white blood cell (WBC) count and automated differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), hemoglobin, hematocrit, RBC indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration).

12.3.2 Serum Chemistry

Blood samples will be collected [redacted]. On Day 1, the blood sample is to be taken within 24 hours prior to infusion. Samples will be analyzed for the following serum chemistry parameters: sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, serum osmolality, and total serum albumin.

12.3.3 Coagulation

Blood samples will be collected [redacted] On Day 1, the blood sample may be taken within 24 hours prior to infusion. Samples will be analyzed for PT and the INR.

12.3.4 Urinalysis

Urine samples will be collected [redacted]. Samples will be analyzed for the following parameters: specific gravity, pH, glucose, protein, blood and ketones (by dipstick and microscopic examination), and urine protein to creatinine ratio.

12.4 Electroencephalogram

Standard EEGs [redacted] will be performed [redacted]. However, additional EEGs may be performed at the discretion of the treating physician, and EEGs [redacted] are only to be performed if clinically indicated. Results from a previous EEG may be provided in lieu of performing an EEG during the Screening Period if the previous assessment was performed within 6 months prior to enrollment and the patient's seizure frequency has not changed significantly since that study. If applicable, the previous EEG findings will be collected and will include the overall interpretation of the specific abnormality (as applicable), and date and time of each evaluation.

12.5 Adverse Event Management

The Investigator is responsible for detecting, assessing, documenting and reporting of all AEs. All AEs will be recorded from the signing of informed consent, until study completion.

Note: There is no time limit for SAEs that are considered causally related.

All observed or volunteered AEs regardless of causal relationship must be reported and recorded in the CRF/eCRF. Adverse events reported by the patient and/or parent or legal guardian and/or identified in response to an open-ended question from study personnel or revealed by observation, physical examination, or other study procedures must be collected and recorded.

12.5.1 Definition of an Adverse Event

An AE is defined as any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the medicinal product or procedure that occurs during the course of the clinical study.

Exacerbations of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition are all to be considered AEs.

Abnormal test findings may be considered AEs. If an abnormal laboratory value is identified, Investigators are strongly encouraged to report a diagnosis, or a sign or symptom rather than an isolated abnormal test value. An abnormal test finding should be documented as an AE if any of the following conditions are met:

- Is associated with a sign or symptom;
- Requires additional diagnostic testing (repeat tests are not considered additional testing);
- Requires a medical or surgical intervention;

- Leads to a change in study dosing outside of the protocol defined dosing or discontinuation from the study;
- Requires significant additional treatment;
- Does not meet any of the conditions above; however, the Investigator or Sponsor considers the result as clinically significant or meeting the definition of an AE.

This definition also includes the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Extravasation
- Medication error
- Occupational exposure

An AE does not necessarily include the following:

- Medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion); the condition that leads to the procedure is the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder);
- Pre-existing diseases or conditions present or detected prior to the Screening evaluation that do not worsen;
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery if planned prior to the start of the study, social and/or convenience admissions).

12.5.2 Definition of a Serious Adverse Event

Any AE that fulfills any one of the criteria listed below must be recorded as an SAE. An SAE is described as any untoward medical occurrence that at any dose:

Results in death

Is life-threatening

Requires hospitalization or prolongation of hospitalization[b]

Hospitalization does not necessarily include the following:

- Rehabilitation/hospice/nursing facility
- Emergency Room/Department visit less than 24 hours
- Elective or preplanned admission/surgery/Day surgery
- Protocol-specified admission
- Admission for a pre-existing condition not associated with either a new AE or with worsening of a pre-existing AE

Results in persistent or significant disability/incapacity

Is a congenital anomaly/birth defect

Is an important medical event[c]

a. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
b. Hospitalization requires inpatient or prolongation of an existing hospitalization. AEs that are associated with hospitalization or prolongation of hospitalization are considered SAEs.
c. Important Medical Event: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency.

Severity and seriousness must be differentiated. Severity describes the intensity of an AE while the term seriousness refers to an AE that has met the criteria for an SAE as described above.

12.5.3 Severity Assessment

An assessment of severity will be made by the Investigator using the following criteria:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concerns with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Change in severity of an AE should be documented based on specific guidance in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE while seriousness refers to an AE that has met the criteria for an SAE.

12.5.4 Causality Assessment

An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded on the CRF/eCRF and any additional forms as appropriate.

The definitions for the causality assessments are as follows:

- Not related (unrelated): This relationship suggests that there is no association between the study drug and the reported event.
- Unlikely related: This relationship suggests that the clinical picture is highly consistent with a cause other than the study drug, but attribution cannot be made with absolute certainty and a relationship between the study drug and AE cannot be excluded with complete confidence.
- Possibly related: This relationship suggests that treatment with the study drug may have caused or contributed to the AE, ie, the event follows a reasonable

temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug but could also have been produced by other factors.

- Probably related: This relationship suggests that a reasonable temporal sequence of the event with the study drug administration exists and the likely association of the event with the study drug. This will be based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the Principal Investigator's clinical experience.
- Definitely related: Temporal relationship to the study drug. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, re-appearance on re- challenge.

12.5.5 Outcome

For all AEs, regardless of causal relationships, the Investigator must follow-up on the outcome of the event until the event or sequelae either resolves or stabilizes.

If a patient experiences a SAE with an outcome of death:

- The SAE resulting in death should have an outcome documented as death/fatal with an end date being the date of death.
- If the patient had additional AEs/SAEs that were ongoing at the time of death, these events would be documented as ongoing with no end date.
- Only 1 event should have an outcome of death/fatal unless an autopsy report or Investigator states otherwise.

12.5.6 Recording Adverse Events

All observed or volunteered AEs regardless of causal relationship must be reported as described in Section 12.5.4.

For all AEs, the Investigator must obtain adequate information for the following:

1. determine the outcome of the AE;
2. determine if the event meets criteria for an SAE;
3. assess the severity of the AE;
4. determine the causality of the AE.

Adverse events must be documented in clear, unambiguous medical term. Study personnel are advised not to use abbreviations or acronyms.

For each AE, record only the diagnosis on the AE page of the CRF/eCRF. Do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available, record each sign and symptom as an AE. When a diagnosis becomes available, study personnel are to update the source document and the AE page of the CRF/eCRF with relevant diagnosis only.

For medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion), the condition/diagnosis that leads to the procedure should be recorded as the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder).

All AEs that later increase in the frequency and/or severity (medical and scientific judgment should be exercised by the Investigator) will be considered new AEs and will be recorded on a new line in source and the CRF/eCRF.

Withdrawal due to an AE or SAE must be clearly differentiated from withdrawal due to other reasons.

12.5.7 Reporting of Serious Adverse Events to Sponsor

All AEs must be assessed by the Investigator to determine if they meet criteria for an SAE. All SAEs must be reported to the Sponsor or designee immediately or within 24 hours of the Investigator or their staff becoming aware of them regardless of the presumed relationship to the study drug.

The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or fax to the contact information provided [redacted]

[redacted]

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information.

Additional follow-up information, if required or available, should be entered into the CRF/eCRF and sent to the Sponsor within 24 hours of the Investigator site or their staff becoming aware of this additional information via the reporting process outlined above. These reporting timelines need to be followed for all initial SAE cases and follow-up versions of the initial cases.

For all SAEs the Investigator must provide the following:

- Clear identification of the Investigator/Reporter with full contact information, country and site number
- Subject identification details (subject's unique study identification number)
- Investigational Medicinal Product(s) administration details (dose and dates) Seriousness criteria
- Appropriate and requested follow-up information in the time frame detailed above
- Causality of the serious events
- Outcome of the serious events
- Medical records and laboratory / diagnostic information

12.5.8 Reporting Requirements

This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor from the Reference Safety Document.

12.5.8.1 Sponsor Reporting Requirements

The Sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria.

12.5.8.2 Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for the study Investigators. It is the PI's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug--related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC (if local) of these additional SAEs. Investigators will receive blinded information unless unblinded information is judged necessary for safety reasons.

13 STATISTICAL METHODS AND PLANNED ANALYSES

13.1 General Considerations

Data collected during the study will be presented in summary tables, figures, or by-patient data listings. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency distributions. No formal hypothesis testing will be performed.

13.2 Determination of Sample Size

At least 4 MoCD Type A patients will be enrolled in the study. The actual sample size will depend on the number of eligible patients currently being treated with rcPMP.

13.3 Analysis Population

Efficacy analyses will be performed on the Full Analysis Set (FAS). Due to the small number of patients, a Per-Protocol Population will not be utilized for this study. The FAS will include all patients who receive at least 1 dose of ORGN001.

Safety analyses will be performed on the Safety Set, defined as all patients who receive at least 1 dose of ORGN001.

13.4 Demographics and Baseline Characteristics

All demographic and baseline characteristics information will be summarized for all patients. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (mean, median, SD, and minimum and maximum).

13.5 Patient Disposition and Treatment Compliance

The number of patients screened, treated, completing the 6-Month Initial Treatment Period, and included in the safety and efficacy analysis sets will be tabulated by counts and percentage of patients. Reasons for any patient withdrawals will be provided.

Treatment compliance with ORGN001 will be presented for all patients.

13.6 Prior and Concomitant Medications

Prior and concomitant medications will be summarized using the Safety Set. Listings of prior and concomitant medications will be produced as will listings of seizure medications.

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug) version 01 September 2013 or higher. Medication summaries will be presented by WHODrug Anatomical Therapeutic Chemical (ATC) and by WHODrug generic name.

13.7 Efficacy Analyses

Efficacy analyses will be performed on the FAS.

13.7.1 Primary Efficacy Analysis

There is no prespecified primary efficacy endpoint in this study. Secondary efficacy analyses are described in Section 13.7.2 [redacted].

13.7.2 Secondary Efficacy Analyses

The secondary efficacy endpoints include:

- 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--III, GMFCS, 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

Baseline is defined as the last available assessment prior to treatment with ORGN001 except for blood and urine biomarkers whereby baseline is defined as the average of all available assessments prior to treatment with ORGN001.

Observed urine and blood SSC levels as well as changes and percentage changes from baseline to the study time points will be summarized. Individual patient plots over time will be produced.

Shifts from baseline in clinical findings from neurologic examination and neuroimaging findings will be presented for the different time points. The frequency of seizures will be summarized.

Observed values and changes in GMFCS, WPPSI, and Bayley-III cognitive, language, and gross and fine motor scores will be summarized.

Growth parameters (weight [kg], length [cm], and head circumference [cm]) will be converted to age-adjusted z-scores and descriptive statistics will be presented for each parameter over time. In addition, the following individual patient's growth charts will be produced as specified in the statistical analysis plan (SAP) with a flag for start of ORGN001 infusion: Weight-for-age percentiles, length-for-age percentiles and head circumference-for-age-percentiles.

[redacted]

13.8 Safety Analyses

Safety analyses will be performed on the Safety Set defined as all patients who receive at least 1 dose of ORGN001.

13.8.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.1 or higher).

Adverse events occurring from the signing of informed consent and prior to the initiation of study drug treatment (pretreatment AEs) will be summarized.

Treatment-emergent AEs are AEs that begin after the start of ORGN001. Treatment-emergent AEs will be summarized by incidence, Preferred Term, System Organ Class (SOC), seriousness, severity, relationship to treatment.

All AEs will be summarized by both event counts and patient counts. For patient counts, if a patient has more than one occurrence of an AE for a specific Preferred Term or SOC, the patient will be counted only once for that Preferred Term or SOC. The most severe occurrence of an AE as well as the most extreme relationship of the AE will be indicated in cases of multiple occurrences of the same AE at onset of the AE.

13.8.2 Laboratory Parameters

Changes from Baseline in laboratory assessments (chemistry and hematology) will be summarized by visit, and shift tables (L [low], N [normal], H [high]) by visit will be produced for clinical laboratory tests.

13.8.3 Physical Examinations and Vital Signs

Physical examinations and Child-Pugh scores (A [a score of 5 to 6], B [a score of 7 to 9], C [a score of 10 or above]) will be summarized by visit. Vital signs (systolic and diastolic BP, temperature, heart rate, and respiratory rate) and changes from baseline in vital signs will be summarized by visit.

13.8.4 Electroencephalograms

The number and percentage of patients with EEG findings will be summarized by visit.

13.9 Pharmacokinetic Analysis

Plasma concentration versus time profiles will be graphically summarized. Non-compartmental PK parameters such as C_{max}, t_{max}, AUC, and $t_{½}$ will be determined if possible, and dose linearity will be explored. Plasma concentration and PK parameter summaries will include descriptive statistics, as appropriate. Details of PK analyses will be presented in an analysis plan.

13.10 Other Statistical Issues

13.10.1 Missing or Invalid Data

If a date of a measurement or an event has a missing or an unknown day, the missing or unknown Day will be substituted by 15 for the calculation of other variables such as age at which the measurement was taken, or the age at the occurrence of an event. If the month or the year of a date is missing, no imputation will take place. In general, other missing or invalid observations will not be replaced or imputed unless otherwise specified in the SAP.

13.10.2 Computing Environment

Efficacy and safety analyses will be performed using SAS for windows, Version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

PK analyses will be performed using Phoenix WinNonlin version 6.3 or higher (Pharsight, Cary, NC, USA).

14 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1 Study Monitoring

A representative of the Sponsor or designee may visit the investigational study site to:

- Determine the adequacy of the facilities and equipment
- Discuss with the Investigators and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a representative of the Sponsor or designee will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigators
- Confirm that facilities and equipment remain acceptable
- Confirm that all patients have been properly consented
- Confirm drug accountability
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs/eCRFs, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs/eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs/eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigators or other staff needs information or advice.

14.2 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection by the Sponsor is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3 Institutional Review Board

The PI must obtain IRB/IEC approval for the investigation. All IRB/IEC approvals, including initial and continued review, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or designee may conduct quality assurance audits (Section 14.2).

16 ETHICS

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP guidelines.

Investigators and other study personnel must comply with all instructions and regulations specified in this protocol and applicable ICH GCP guidelines and must conduct this study in accordance with all local, federal, and regulatory agency regulations.

In accordance to ICH guidelines, pediatric participation in these studies should occur in qualified pediatric centers, with personnel who are properly trained and experienced in studying the pediatric population and in evaluating and managing potential pediatric AEs. Site personnel should be knowledgeable and skilled in dealing with the pediatric population and its age- appropriate needs and be encouraged to use measures that minimize discomfort of procedures (e.g., topical anesthesia to place IV catheters, use of indwelling catheters instead of repeated venipunctures for blood sampling, and collection of some protocol-specified blood samples when routine clinical samples are obtained).

16.1 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the study.

No modifications to the protocol should be made without the approval of both the Investigator and the Sponsor. Changes that significantly affect patient safety, the scope of investigation, or the scientific validity of the study will require IRB/IEC notification prior to implementation, except where the modification is necessary to eliminate an apparent immediate hazard to patients. Any deviations from protocol must be fully documented. The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2 Data Monitoring Committee Review

An independent DMC will be appointed by the Sponsor [redacted] who have no direct relationship with the study.

Prior to each scheduled dose escalation, the SRC chair will convene the DMC to review laboratory and clinical data in conjunction with the SRC to determine if dose escalation is appropriate (Section 3.4).

Final decisions regarding the conduct of the study will be made by the Sponsor after consultation with the DMC. All appropriate regulatory authorities and ECs will be notified of any significant action.

The DMC may be asked to provide medical and ethical guidance related to the conduct of the study as described above. The DMC will review study information as outlined in the DMC charter, which is maintained separately from the study protocol.

Each member of the DMC will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interest as a condition for membership on the board.

16.3 Written Informed Consent

The PIs at each center will ensure that the patient's parent or legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The patient's parent or legal guardian must also be notified that they are free to discontinue their child from the study at any time. The parent or legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated ICF must be obtained before conducting any study procedures.

The PIs must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient's parent or legal guardian.

Should new information become available during the conduct of the study that might impact parent or legal guardian willingness to continue participation in the study, the parent or legal guardian will be notified in a timely manner about the new information and asked to sign a new ICF.

16.4 Patient Data Protection

Prior to the performance of any study-related procedures, the patient’s parent or legal guardian must authorize the release and use of protected health information as required by local, federal and regulatory agency law.

CRFs/eCRFs will be completed at the site either on paper or in the electronic data capture system. Copies of pertinent records in connection with the study, including patient charts and laboratory data, will be made available to the Sponsor or designee on request in a timely manner throughout the course of the study, with due precaution toward protecting patient privacy.

17 DATA HANDLING AND RECORDKEEPING

17.1 Inspection of Records

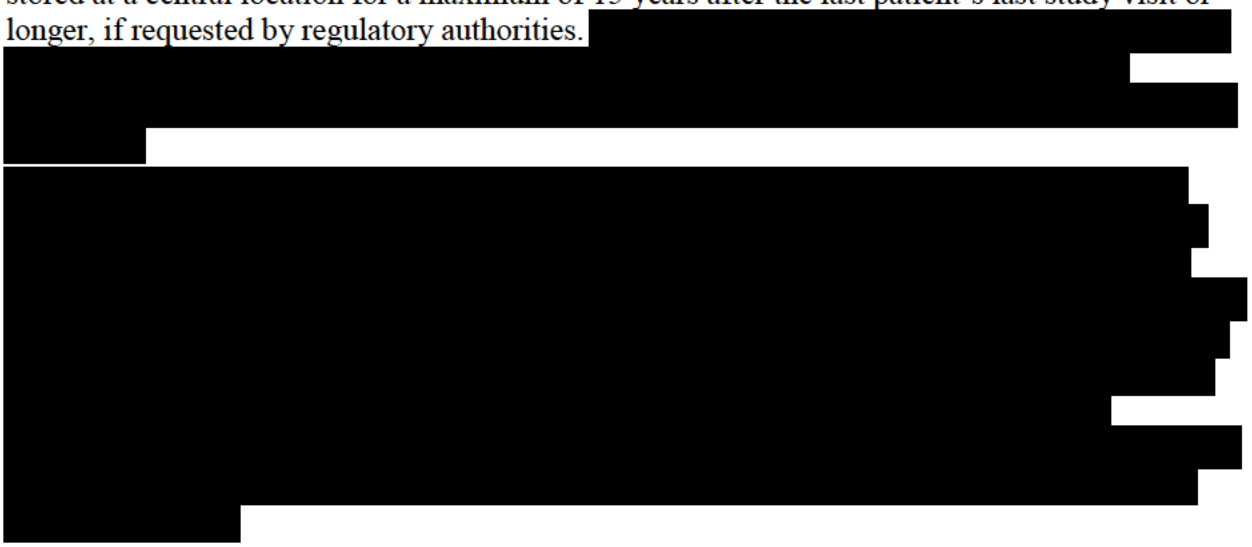
The Sponsor or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

17.2 Retention of Records

The PI must maintain all documentation relating to the study in accordance with local retention requirements, or for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records. No records may be destroyed without Sponsor written approval.

17.3 Retention of Biological Samples

If a patient's parent or legal guardian has/have provided consent for long-term storage of biological samples, and if permitted by local regulatory authorities, any remaining sample will be stored at a central location for a maximum of 15 years after the last patient's last study visit or longer, if requested by regulatory authorities.



The samples and data for biochemical analysis in this study will be single coded. The link between the patient enrollment number and the biochemical results will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant samples for analysis, facilitate correlation of biochemical results with clinical data, allow regulatory audit, and to trace samples for destruction in the case of withdrawal of consent when the patient or consenting guardian has requested disposal/destruction of collected samples not yet analyzed.

If a patient's parent or legal guardian withdraws consent to the use of donated biological samples, the samples will be destroyed, and the action will be documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

17.4 Data Privacy

The Sponsor will make every effort to protect patient privacy. For all study data collection, patients will be identified by a unique patient number and date of birth in regions where permitted. The results from this study may be presented at meetings or in articles. However, patient name or initials that could identify a patient will not be used in any such meetings or articles.

18 PUBLICATION POLICY

The full terms for publication are outlined in the Clinical Study Agreement, Statement of Agreement, or Master Clinical Study Agreement. Publication terms permit publication only after publication of multicenter results and require that any data to be submitted for publication including abstract submissions or presentations, be submitted to the Sponsor for review at least 30 days prior to submission.

19 LIST OF REFERENCES

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20 APPENDICES

- Appendix A Blood Sampling Volumes (European Commission2008; European Medicines Agency (EMA) 2009)
- Appendix B Blood Sampling Volumes Table (Screening Through Month 6)
- Appendix C Blood Sampling Volumes Table (Extension Period and Safety Follow- Up Visit)
- Appendix D Blood Sampling Volumes for Unscheduled Dose Adjustment

Appendix A. BLOOD SAMPLING VOLUMES

[redacted] In particular, an alternative blood sampling schedule for infants weighing less than 10 kg, for whom less blood volume should be collected, must be used [redacted].

The following procedures for blood collection should be adhered to:

1. Number of attempts: The number of attempts for sampling blood is limited to 3 times per day. This means that after 3 punctures for collection of blood have been performed and no or insufficient blood could be collected, no other puncture will be done on the same day.

Volume of blood samples: Per study patient, the study-related blood loss (including any losses in the collection procedure) should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight. Three percent (3%) is 2.4 mL blood per kg of body weight. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. If the required blood volume cannot be obtained due to the above- mentioned safety limits, priority will be given to safety-relevant investigations.

Eutectic mixture of local anesthetics (EMLA) cream/plaster: To minimize the possible pain and discomfort due to the collection of blood, the Investigator should apply an EMLA cream/plaster at the site of puncture.

Appendix B. BLOOD SAMPLING VOLUMES TABLE (SCREENING THROUGH MONTH 6)

Table 10: Blood Sampling Volumes (Screening Through Month 6)

		Study Day	[redacted]
Sample	**Marker or Specific Time**	[redacted]	
Genotype (if not previously done)			
Serum Chemistry			
Hematology			
Coagulation			
Biochemical PD Markers	[redacted]e		
[redacted]			
ORGN001 levels (PK)	Preinfusion		
	EOI		
	0.5 hrs. after the EOI		
	1 hr. after the EOI		
	2 hrs. after the EOI		
	3 hrs. after the EOI		
	4 hrs. after the EOI		
	5 hrs. after the EOI		
	24 hrs. after the EOI[2]		
[redacted]			

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the

Investigator should provide justification for the deviation. [redacted]

[2] An optional venous blood sample may be collected at 24 hours after the EOI for PK and PD assessments.
Abbreviations: EOI = end of infusion; [redacted] mL = milliliters; PD = pharmacodynamic; PK = pharmacokinetics; SSC = S-sulfocysteine.

Appendix C. --BLOOD SAMPLING VOLUMES (EXTENSION PERIOD AND SAFETY FOLLOW-UP VISIT)

Table 11: Sample Volume Collection During the Extension Period and Safety Follow--Up Visit

Assessment	Extension Period	[redacted]
Month	[redacted]	
Visit Window (Days)		
Serum chemistry		
Serum hematology		
PD sampling, predose blood[1]		
PD sampling, blood[1]		
ORGN001 levels (PK)[2]		

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. [redacted]

[1] Collect venous blood samples for SSC, [redacted] biomarker analysis. [redacted]

[2] Pharmacokinetics will be collected at 1 visit between Month 7 and the last month of the Extension Period at the EOI and 4 hours post EOI.

[redacted]

Abbreviations: EOI = end of infusion; mL = milliliters; PD = pharmacodynamic; PK = pharmacokinetics; SSC = S-sulfocysteine.

Appendix D. BLOOD SAMPLING VOLUMES FOR UNSCHEDULED DOSE ADJUSTMENT

Table 12: Sample Volume Collection for an Unscheduled Dose Adjustment

Assessment	Specific Time	First Day Adjusted Dose is Administered	[redacted] Follow-Up Visit	[redacted]
Serum chemistry	Any time during study visit	[redacted]		
Serum hematology				
PD sampling, blood	3 to 4 hours after the EOI			
PK sampling	EOI			
PK sampling	3 to 4 hours after the EOI			
[redacted]				

Note regarding blood samples: The total blood volume will not exceed the amount considered acceptable for the patient's clinical condition and the institution's guidelines [redacted]. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation. [redacted]

Abbreviations: EOI = end of infusion; meds = medications; PD = pharmacodynamics; PK= pharmacokinetics.