NCT Number: NCT02629393

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-202

A Phase 2/3, Multicenter, Multinational, Open-Label Study to Evaluate the Efficacy and Safety of ORGN001 (formerly ALXN1101) in Neonates, Infants, and Children with Molybdenum Cofactor Deficiency (MoCD) Type A

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]
Medical Monitor:	[redacted] Origin Biosciences, Inc. [redacted]
IND Number:	117502
EudraCT Number:	2013-002702-30
Version:	5.0
Date of Original Protocol:	27 August 2015
Date of Protocol Amendment 1:	24 February 2016
Date of Protocol Amendment 2:	15 February 2019
Date of Protocol Amendment 3:	14 November 2019
Date of Protocol Amendment 4:	29 January 2020

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: **A Phase 2/3, Multicenter, Multinational, Open-Label Study to Evaluate the Efficacy and Safety of ORGN001 (formerly ALXN1101) in Neonates, Infants, and Children with Molybdenum Cofactor Deficiency (MoCD) Type A**

PROTOCOL NUMBER: ALXN1101-MCD-202 Amendment 4

[redacted] _____ 1/30/2020

Date

Chief Medical Officer
Origin Biosciences, Inc.

[redacted] _____ 2/3/2020

Date

Senior Director, Regulatory Affairs
Origin Biosciences, Inc.

[redacted] _____ 2/3/2020

Date

Senior Director, Clinical Operations
Origin Biosciences, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure for ORGN001. I have read and understood all clinical and administrative sections of the ALXN1101-MCD-202 protocol, entitled "A Phase 2/3, Multicenter, Multinational, Open-Label Study to Evaluate the Efficacy and Safety of ORGN001 (formerly ALXN1101) in Neonates, Infants, and Children with Molybdenum Cofactor Deficiency (MoCD) Type A," and agree to conduct the study in accordance with this protocol, all applicable government regulations, and the principles of the World Medical Association Declaration of Helsinki, where applicable. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

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 Lead	[redacted]	Origin Biosciences, Inc. [redacted]
Responsible Physician	[redacted]	Origin Biosciences, Inc. [redacted]
Serious Adverse Event Reporting	[redacted]	

1. SYNOPSIS

Name of Sponsor/Company: Origin Biosciences, Inc. (Origin)	
Name of Investigational Product: ORGN001	
Name of Active Ingredient: Cyclic pyranopterin monophosphate monohydrobromide dihydrate	
Title of Study: A Phase 2/3, Multicenter, Multinational, Open-Label Study to Evaluate the Efficacy and Safety of ORGN001 (formerly ALXN1101) in Neonates, Infants, and Children with Molybdenum Cofactor Deficiency (MoCD) Type A	
Study center(s): This will be a multicenter, multinational study with approximately 10 investigational study centers.	
Principal Investigator: [redacted] **Investigators:** A list containing all Investigators and their contact information will be provided when site selection is completed.	
Study period (months): approximately 36 months (long-term follow-up until approval or decision reached on further development) Estimated date first patient enrolled: 1Q2016 Estimated date last patient completed: 4Q2022	**Phase of development:** 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). Molybdenum cofactor is essential for proper functioning of the enzymes sulfite oxidase (SO), xanthine oxidoreductase, and aldehyde oxidase. The loss of SO activity is responsible for the severe and rapidly progressive neurologic damage seen in neonates presenting with MoCD. Less frequently, older infants and children may present with neurologic symptoms related to MoCD such as seizures, movement disorder and developmental delay/disability that appears to have a less rapidly evolving course.

Although there are three types of MoCD, two-thirds of MoCD patients have Type A, which is due to a mutation in the *MOCS1* gene localized on chromosome 6p21.2. In MoCD Type A, the first of four synthetic steps in the formation of molybdenum cofactor is interrupted, and guanosine triphosphate (GTP) cannot be converted into cyclic pyranopterin monophosphate (cPMP). Diagnosis of MoCD Type A in neonates is based on clinical and laboratory presentation (eg, seizures, exaggerated startle response, high-pitched cry, intracranial hemorrhage, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or S-sulfocysteine [SSC], or low or absent uric acid in the urine or blood) and is then confirmed by genetic testing. The clinical presentation after the neonatal period appears to be more heterogeneous and may progress less rapidly.

The incidence of MoCD is estimated to be between 1/100,000 and 1/200,000 newborn babies worldwide. Affected individuals usually present as neonates with severe symptoms that are observed as part of standard clinical practice. These include, but are not limited to, intractable seizures, burst-suppression on electroencephalogram (EEG), exaggerated startle reactions, axial hypotonia, limb hypertonia, and feeding difficulties. Death commonly occurs in the neonatal period, and patients who survive that period may develop a severe static encephalopathy and developmental delays 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 for MoCD.

Results from nonclinical pharmacology studies with ORGN001 suggest that the metabolic derangement in MoCD Type A could be corrected by administration of synthetic cPMP. Restoration of MoCo biosynthesis and SO activity is expected to result in correction of the metabolic pathways that would otherwise lead to accumulation of toxic metabolites that cause 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; formerly known as Orphatec Pharmaceuticals GmBH), which has been administered on a named-patient basis following individual physician requests. Published individual case reports suggest that intravenous (IV) administration of rcPMP restores MoCo-dependent enzyme activities, reduces concentrations of disease biomarkers (eg, SSC in urine), and has the potential to improve neurologic outcome.

In addition to clinical experience with rcPMP, [redacted] healthy volunteers received ORGN001 in a first-in-human study, ALXN1101-MCD-101, in which ORGN001 was well tolerated at doses [redacted] administered IV. [redacted] Across both cohorts, no deaths or life-threatening TEAEs occurred, and no one withdrew due to a TEAE. [redacted] To date, ORGN001 has been well-tolerated, and there have been no serious adverse reactions with causality attributed to ORGN001 reported, and no patient has withdrawn or discontinued as a result of an adverse event (AE).

This study is designed to evaluate the efficacy and safety of ORGN001 in neonates, infants, and children with MoCD Type A.

Objectives

Primary:

- To evaluate the safety and efficacy of ORGN001 in neonate, infant, and pediatric patients with MoCD Type A who are either treatment-naïve or who have received compassionate use ORGN001

Secondary:

- [redacted]
- To evaluate the effect of ORGN001 on growth and development using age-appropriate assessments
- To evaluate the effect of ORGN001 on pediatric measures of functional ability and activities of daily living
- [redacted]

[redacted]

Endpoints

Primary Efficacy Endpoint:

- Overall survival (OS)

Secondary Efficacy Endpoints:

- [redacted]
- Changes in growth parameters (height, weight, body mass index [BMI], head circumference) through Month 12
- Feeding pattern assessments through Month 12
- Gross Motor Function Classification System Expanded and Revised (GMFCS-E&R) results through Month 12
- Assessments of the Bayley Scales of Infant Development® – Third Edition (Bayley-III) Cognitive and Motor Scales as measured through Month 12
    - For children aged 3 and above, for whom the Bayley-III is no longer appropriate, the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) will be administered.
    - For patients with severe developmental delay, the WPPSI may not be an appropriate assessment, and therefore, the Bayley-III may be administered instead.
- Functional ability and activities of daily living, measured by the Pediatric Evaluation of Disability Inventory (PEDI) through Month 12
- Gross Motor Function Measure (GMFM)-88 results through Month 12

[redacted]

[redacted]

Safety Endpoints:
The type, frequency, severity, timing, and relationship to study drug to any AEs, serious AEs (SAEs), and changes in vital signs, electrocardiograms, and safety laboratory tests

Methodology:
This Phase 2/3, multinational, multicenter, open-label study is designed to evaluate the efficacy and safety of daily IV administration of ORGN001 to neonates, infants, and children with MoCD Type A. For the purposes of this study, neonate patients are defined as those from 1 to 28 days of age (inclusive) at the time of first ORGN001 dose administration, with day 1 of age corresponding to the day of birth. Infants are defined as those from 29 days to <2 years of age. Children are defined as those from 2 to 5 years of age (inclusive). Patients must be treatment-naïve or may have previously received ORGN001 through the expanded access program (EAP).

In neonate patients with signs and symptoms consistent with MoCD Type A, treatment should be initiated as soon as feasible, in an effort to prevent the irreversible neurologic damage that is expected to occur.

- Eligible neonates with a prenatal diagnosis of MoCD Type A will undergo Screening/Baseline assessments (eg, brain imaging) prior to or as soon as possible after birth and prior to receiving their first daily IV infusion of ORGN001. Given the life-threatening and devastating nature of the disease and the potential for a favorable benefit:risk profile for treatment with ORGN001, patients with a prenatal diagnosis may be treated prior to onset of signs and symptoms associated with MoCD Type A. Additionally, if it is not possible to obtain brain imaging prior to treatment, the priority would be to treat the neonate and obtain brain imaging as soon as feasible afterwards. For those patients, the patient's legal guardians (per country-specific requirement) may be asked prior to delivery to provide informed consent for participation in the study. [redacted]

- Eligible neonates who do not have a prenatal diagnosis of MoCD Type A but who have onset of the signs and symptoms that may serve as the basis for diagnosis will undergo Screening/Baseline assessments as soon as possible prior to receiving their first daily IV infusion of ORGN001. Data from procedures conducted as part of standard of care prior to study participation may be collected as part of Medical History. Genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy.

Eligible patients beyond the neonatal period with genetically confirmed evidence of MoCD Type A, a biochemical profile, and clinical picture consistent with MoCD Type A may also be enrolled following completion of Screening/Baseline assessments. Data from procedures conducted as part of standard of care prior to study participation may be collected as part of Medical History. Genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases.

In all patients, ORGN001 will be administered daily from Day 1 of the study. Completion of a brain MRI may be delayed until after the initiation of ORGN001 if not feasible to complete prior to study drug initiation. [redacted] patients will continue to receive daily infusions of ORGN001 at home [redacted] and will return to the clinic for study visits for safety, efficacy, and PK assessments.

A Safety Review Committee (SRC) and an external, independent Data Monitoring Committee (DMC) will review safety, efficacy, and PK data for this study periodically and will be consulted on an ad hoc basis for individual cases. Continuation of ORGN001 treatment will be based on treating physician assessment as well as recommendations by the combined SRC and DMC regarding the benefit: risk assessment for each patient. [redacted]

Patients with a genetic diagnosis other than MoCD Type A will be discontinued from ORGN001 treatment as they are not expected to receive any treatment benefit. Patients who discontinue prematurely from treatment will be followed for 28 days, [redacted].

Dose Selection Strategy: A population PK (PopPK)-based approach has been utilized to create a dosing scheme that targets the higher end of the originally acceptable exposure range for ORGN001 (no observable adverse effect level [NOAEL]: AUC [redacted] at the highest dose studied in the original toxicology study that was limited by solubility issue. Since then, higher doses have been studied and were all well tolerated in rats and dogs using an improved IV formulation. [redacted]

[redacted]

A PopPK model was derived to characterize ORGN001 clinical PK in healthy adult volunteers (Study ALXN1101-MCD-101) and children with MoCD Type A (Study ALXN1101-MCD-201). Due to [redacted] renal clearance of ORGN001 in adults (Study ALXN1101-MCD-101), a function was included to account for the expected impact of

renal function maturation (Rhodin 2009) on ORGN001 PK in neonate patients. [redacted]

Dosing will be based upon the gestational age (GA) of the patient. [redacted] Following Investigator and Safety Review Committee (SRC) reviews (as well as Data Monitoring Committee [DMC] review of data prior to the first dose adjustment for each patient as well as subsequent periodic review of cumulative data); recommended dosing may follow the guidance in Table 3.

The dosing strategy in Table 3 has been simplified compared to the original guidance. This is justified given 1) the much greater safety margin with respect to the NOAEL described above; 2) the excellent safety profile of ORGN001 thus far with all patients tolerating the maximum 1200 µg/kg dose well and no safety signals identified [redacted]; and 3) the fact that dose increments [redacted] were well tolerated in Study ALXN1101-MCD-201.

Table 3: Dosing and Dose Adjustment for Term and Preterm Neonate Patients, Older Infants, and Children in Study ALXN1101-MCD-202

Study Day	Term Neonate (GA ≥ 37 weeks) and Older Infants/Children Dose (µg/kg/day)	Preterm Neonate (GA < 37 weeks) Dose (µg/kg/day)
Day 1	700	525
Day 28	1000	900
Month 3	1200	1200

Abbreviations: GA=gestational age.

Doses may be adjusted based on drug-related AEs or changes in clinical parameters, laboratory data, or PK findings and will occur following consultation with the medical monitor and, if applicable, with the SRC.

Day 1 PK samples will be analyzed, and PK assessments will be completed for a DMC meeting that will be scheduled prior to the first dose adjustment. If the Day 1 AUC is greater than the upper of the target AUC range [redacted], there will be a dose recommendation for a decrease by the percentage that the individual AUC is greater than the midpoint of the target AUC range [redacted].

If the Day 1 AUC is less than the lower limit of the target AUC range [redacted], there will be a dose recommendation for an increase by the percentage that the individual AUC is less than the midpoint of the target AUC range [redacted].

Number of patients (planned):
There will be no minimum or maximum number of patients for this study.

Diagnosis and main criteria for inclusion
Inclusion criteria:
Patients must meet all of the following inclusion criteria to be considered for enrollment in this study:

- Male or female neonatal patient (1 to 28 days of age [inclusive] at the time of ORGN001 administration, with day 1 of age corresponding to the day of birth) or infant (29 days to <2 years of age) or child (2 to 5 years of age [inclusive]) with MoCD Type A, previously untreated with ORGN001 or treated with ORGN001 through the EAP
- In neonates, diagnosis of MoCD Type A, based on:
  - Prenatal genetic diagnosis, or
  - Onset of clinical and/or laboratory signs and symptoms consistent with MoCD Type A (eg, seizures, exaggerated startle response, high-pitched cry, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or SSC, elevated xanthine in urine or blood, or low or absent uric acid in the urine or blood) within the first 28 days after birth
- In infants or children, diagnosis of MoCD Type A, based on:

- Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A
- Parent or legal guardian must have signed the informed consent form (ICF) prior to any study procedures being performed.

Exclusion criteria:
Patients will be excluded from participating in the study if they meet any of the following criteria:

- Diagnosis other than MoCD Type A (may be determined after the initiation of study drug)
- Condition that is considered by the treating physician to be a contraindication to therapy, including evidence of abnormalities on brain imaging not attributable to MoCD Type A, or that might otherwise interfere with the patient's participation in the study, pose any additional risk for the patient, or confound patient assessments
- Antenatal and/or postnatal brain imaging prior to initiation of treatment with ORGN001 that indicates cortical or subcortical cystic encephalomalacia, clinically significant intracranial hemorrhage, or other abnormalities on brain imaging determined by the treating physician to be clinically significant
- Modified Glasgow Coma Scale (mGCS) for Infants and Children score of less than 7 for more than 24 hours (does not apply to children less than 1 day in age).

Investigational product, dosage, and mode of administration:
ORGN001, which is a synthetic form of cPMP, is supplied as a sterile, [redacted] white to slightly yellow lyophilized powder [redacted] to be reconstituted using [redacted] sterile Water for Injection and administered by IV infusion.

Dosing with ORGN001 in neonates will be based upon the schedule presented in Table 3. Following Investigator and SRC/DMC review (prior to the [redacted] dose adjustment of each patient [redacted] as well as subsequent periodic reviews of cumulative data), doses may be adjusted, based on drug-related AEs, changes in clinical parameters, or PK findings.

Dosing with ORGN001 in infants and children will be based upon the schedule presented in Table 3. Following Investigator and SRC/DMC review (prior to the [redacted] dose adjustment of each patient [redacted] as well as subsequent periodic reviews of cumulative data), doses may be adjusted, based on drug-related AEs, changes in clinical parameters, or PK findings.

Duration of treatment:
ORGN001 will be administered once daily throughout the study.

Reference therapy, dosage, and mode of administration:
None

Criteria for evaluation
Refer to the efficacy, safety, and PK endpoints for a description of the assessments to be analyzed.

Statistical methods:
Efficacy, safety, and PK[redacted] data will be analyzed in this study.

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

Efficacy analyses will be performed on two modified Full Analysis Sets (Neonate mFAS and Pediatric PmFAS), as well as the Full Analysis Set.

Safety: The incidence of TEAEs 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 laboratory assessments (chemistry, hematology, and urinalysis) will be summarized. Incidence of abnormalities for clinical laboratory assessments (serum chemistry and hematology) will be summarized by visit.

Primary Efficacy Endpoint Analyses: Overall survival is defined as the interval in months from the date of birth to the date of death or date last known alive (patients still on study will be censored at the data cut-off), whichever occurs first.

Secondary Efficacy Endpoints Analyses: [redacted]

Body weight, length, head circumference, and BMI will be analyzed by converting each parameter to age-adjusted z-scores and age percentiles, and descriptive statistics will be presented for each parameter through Month 12.

Feeding patterns through Month 12 will be analyzed via the frequency and percentages of each feeding method at each visit where feeding pattern was recorded.

Changes in motor function through Month 12 will be summarized based on data from the administration of the GMFCS-E&R, which is a 5-level classification system that classifies gross motor functional capabilities and limitations as usual performance in the home, school, and community setting.

The Bayley-III Cognitive and Motor scaled scores and composite scores, as well as percentile ranks, and age equivalents, will be summarized through Month 12. Where appropriate, the WPPSI-IV will be used instead of the Bayley-III.

Changes in PEDI standard and scaled scores will be summarized by self-care, mobility, and social function domains through Month 12.

Changes in acquisition of motor development milestones will be summarized through Month 12 based on data from the administration of the GMFM-88, which measures patient-initiated motor activities in 5 dimensions: Lying and Rolling; Sitting; Crawling and Kneeling; Standing; and Walking, Running, and Jumping. A percent score can be obtained for each dimension and for the total of all GMFM dimensions. Patients who use mobility aids and/or orthoses will be assessed without those aids.

[redacted]

[redacted]

SUMMARY OF CHANGES

Table 4: Changes Between Amendment 1 and Amendment 3

Section	Description of Change
Cover page	• Protocol title updated to reflect addition of infants and children to the study population. (This change has been carried through to all other locations in which the protocol title is shown.) • Updated to reflect new sponsor, Origin Biosciences, Inc., who acquired the program from Alexion Pharma GmbH in September 2018. • Updated responsible study personnel. • The protocol number ALXN1101-MCD-202 will remain unchanged.
Investigational medicinal product name	On the acquisition of ORGN001 by Origin Biosciences, Inc., the IMP ALXN1101 (cyclic pyranopterin monophosphate monohydrobromide dihydrate) has been renamed ORGN001.
Sponsor Signature Page	• Updated responsible medical officer. • Added additional signatories.
Procedures in Case of Emergency	Updated contact information for reporting SAEs.
2 Synopsis	[redacted] • The study period has been adjusted to accommodate long-term follow-up until approval or decision reached on further development of ORGN001, and last patient completion date has been adjusted to 4Q2022. • The study background/ rationale, study objectives, endpoints, methodology, inclusion/exclusion criteria, and statistical methods have been updated to reflect the changes detailed in sections below that have been made to expand the study subject population to include older infants and children with MoCD.
2.1 Background	The background has been revised to include information on older children and infants with MoCD.
2.2 Rationale for the Study	Additional text: "Responsibility for the development of ORGN001 in the treatment of MoCD Type A was assumed by Origin Biosciences, Inc, in September 2018."
2.3 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."

Section	Description of Change
2.4 Rationale for Patient Population	Additional text: • "However, the clinical presentation after the neonatal period appears to be more heterogeneous and may progress less rapidly in some patients. In an effort to more fully characterize the potential impact of ORGN001 in MoCD Type A, the study has thus been modified to include infants and children with MoCD Type A, who are treatment-naïve or may have previously received ORGN001 through the early access program (EAP). Infants are defined as those from 29 days to <2 years of age in Amendment 3. Children are defined as those from 2 to 5 years of age (inclusive)." • "In infants or children, eligibility will be determined by confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A."
2.5 Rationale for Proposed Dosing	Additional text and tables have been added on the basis of a population PK (PopPK) model: • "Since then, higher doses have been studied and were all well tolerated in rats and dogs using an improved IV formulation. Accordingly, the revised NOAEL values in a [redacted] rat study provide a considerable increase in the safety margins [redacted]." • "The dosing strategy in Table 9 has been simplified compared to the original guidance. This is justified given 1) the much greater safety margin with respect to the NOAEL in the [redacted] rat study described above; 2) the excellent safety profile of ORGN001 thus far with all patients tolerating the maximum 1200 µg/kg/day dose and no safety signals identified [redacted]; and 3) the fact that dose increments [redacted] were well tolerated in Study ALXN1101-MCD-201."
2.6 Rationale for Overall Study Design	Additional text: "Less frequently, older infants and children may present with neurologic symptoms related to MoCD such as seizures, movement disorder, and developmental delay/disability that appears to have a less rapidly evolving course."
3.1 Objectives	• Primary objective updated to include infants and pediatric patients who are either treatment-naïve or who have received compassionate use ORGN001. • Secondary objectives [redacted] encompass evaluation of [redacted] the effect of ORGN001 on growth and development using age-appropriate assessments, [redacted].

Section	Description of Change
3.2 Endpoints	Primary efficacy endpoint modified to overall survival. Secondary efficacy endpoints modified to include variables (eg, changes in growth parameters, feeding pattern assessments, and developmental assessments) appropriate to the expanded study subject population and study period. [redacted]
4.1 Overall Study Design	Additional text: • "Infants are defined as those from 29 days to < 2 years. Children are defined as those from 2 years to 5 years (inclusive) at the time of informed consent." [redacted] • "Eligible patients beyond the neonatal period with genetically confirmed evidence of MoCD Type A, a biochemical profile, and clinical picture consistent with MoCD Type may also be enrolled following completion of Screening/Baseline assessments." • "Data from procedures conducted as part of standard of care prior to study participation may be collected as part of Medical History. Genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases." • "Due to the rare nature of the disease and no currently available treatment, patients exceeding 36 months of treatment may continue to receive study drug until ORGN001 becomes commercially available or development has stopped. For patients receiving ORGN001 past month 36, a safety visit will occur [redacted]. Assessments performed during those visits are for the purposes of ongoing safety to receive ORGN001 and may only occur if ORGN001 is not yet commercially available for the patient." [redacted]
4.2 Number of Patients	Revised so that no minimum or maximum number of patients is projected for enrollment in the study.

Section	Description of Change
4.3 Study Assessments	• Updated to include any differences in assessment between neonates, infants, and children as based on the Schedules of Assessments (which are referenced throughout rather than all information being duplicated in these subsections). • Vital signs assessment [redacted] specified as predose (Section 4.3.6). Additional systolic and diastolic blood pressure measurements to be collected [redacted] 30 minutes post-EOI was added as a time point. • Serum osmolality added as a parameter of blood chemistry/hematology sample analysis to align with the assessment table and CRF (Section 4.3.8). • Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) added as an alternative to the Bayley-III for those patients developmentally beyond the Bayley-III (Section 4.3.12).
5 Schedules of Assessments: (Screening/Baseline and 12-Month Study Period)	• [redacted] • WPPSI-IV listed as alternative to the Bayley-III. • [redacted] • Brain ultrasound specified for neonates only. • Footnote added that additional systolic and diastolic blood pressure measurements are to be collected [redacted] approximately 30, 60, 90, and 120 minutes post-EOI and at 6 and 12 hours post-EOI.
5 Schedules of Assessments: (Long-Term Treatment Period and Safety Follow Up)	• WPPSI-IV listed as alternative to the Bayley-III. • Safety Follow-up ET Visit column has had developmental assessments added as included and a footnote made stating that these assessments will only occur [redacted] for children continuing on ORGN001 past the study follow up period where ORGN001 is not commercially available.
5 Schedules of Assessments: (Following Recommendation by the Safety Review Committee for an Unscheduled Dose Adjustment)	• PD blood sampling to occur predose. • PK blood sampling to occur at EOI (±5 minutes), 1 to 2 hours after the EOI, and 3 to 4 hours after the EOI.
6.3 Definition of Study End	Additional text: "Due to the rare nature of the disease and no currently available treatment, patients exceeding 36 months of treatment may continue to receive study drug until ORGN001 becomes commercially available or development has stopped."

Section	Description of Change
7.2 Patient Inclusion Criteria	Additional text for the first criterion: "or infant (29 days to < 2 years of age) or child (2 to 5 years of age [inclusive]) with MoCD Type A, previously untreated with ORGN001 or treated with ORGN001 through the EAP" Additional criterion added: • In infants or children, diagnosis of MoCD Type A, based on: – Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A
[redacted]	[redacted]
[redacted]	[redacted]
10 Pharmacodynamics Assessments	Timing of additional blood and urine sample collection following unscheduled dose adjustments changed to be as follows: On the first day the adjusted dose is administered, the patient will be administered study drug in-clinic, and a pre-dose blood sample will be collected on the [redacted] day of the dose adjustment [redacted]. A urine sample will be collected at any time during [redacted] the dose adjustment visit.
11 Pharmacokinetics Assessments	• PK samples were specified for collection [redacted]. • An additional PK sample was added to occur at 1 to 2 hours after EOI on regularly scheduled collection days, on any day [redacted] of an unscheduled dose adjustment.
[redacted]	[redacted]
13.5.8 Reporting of Serious Adverse Events to Sponsor	[redacted] Additional text: "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"
[redacted]	[redacted]

Section	Description of Change
	[redacted]
14.1 Determination of Sample Size	[redacted] "There will be no minimum or maximum number of patients for this study. The final sample size and determination of study success relative to efficacy will depend on the overall survival rate as each successive patient reaches study completion."
14.2 Analysis Populations	A Full Analysis Set (FAS) has been defined for performance of the efficacy analyses; the FAS is defined as patients with a confirmed diagnosis of MoCD Type A who have no antenatal and/or postnatal brain imaging prior to initiation of treatment with ORGN001 that indicates cortical or subcortical cystic encephalomalacia or clinically significant intracranial hemorrhage. Additional text: "Additionally, two modified Full Analysis Sets (mFAS) will be used to support the analyses on the FAS: • Neonate mFAS (NmFAS), [redacted] • Pediatric mFAS (PmFAS), [redacted]
14.3 Efficacy and Pharmacokinetic Endpoints	**Primary Efficacy Endpoint:** Changed to be overall survival. **Secondary Efficacy Endpoints:** [redacted] • Changes in growth parameters (height, weight, BMI, head circumference) through Month 12 • Feeding pattern assessments through Month 12 • GMFCS-E&R results through Month 12 • GMFM-88 results through Month 12 [redacted]

Section	Description of Change
	[redacted]
14.4 Demographics and Baseline Characteristics	Fas, NmFAS, and PmFAS added.
14.7 Efficacy Analyses	Fas, NmFAS, and PmFAS added.
[redacted]	[redacted]
14.7.2 Primary Efficacy Analysis	"The primary efficacy analysis will summarize overall survival, defined as the interval in months from the date of birth to the date of death or date last known alive (patients still on study will be censored at the data cutoff date), whichever occurs first. The analysis of OS will be based on the Kaplan-Meier methodology for estimation of survival parameters. The median duration of OS will be estimated based on the 50th percentile of the Kaplan-Meier distribution; additional summary statistics, including the 25th and 75th percentiles, 95% confidence intervals (CIs) on the median and the other percentiles and proportion of censored patients. The analysis of OS will be done using the FAS, the NmFAS, and the PmFAS."
14.7.3 Secondary Efficacy Analyses	[redacted]

Section	Description of Change
	Text added: • "Body weight, length, head circumference, and BMI will be analyzed by converting each parameter to age-adjusted z-scores and age percentiles, and descriptive statistics will be presented to each parameter through Month 12." • "Changes in motor function through Month 12 will be summarized based on data from the administration of the GMFCS-E&R, which is a 5-level classification system that classifies gross motor functional capabilities and limitations as usual performance in the home, school, and community setting." • "The Bayley-III Cognitive and Motor scaled scores and composite scores, as well as percentile ranks, and age equivalents will be summarized through Month 12. Where appropriate, the WPPSI-IV will be used instead of the Bayley-III." • "PEDI standard and scaled scores will be summarized by self-care, mobility, and social function domains through Month 12."
[redacted]	[redacted]
[redacted]	
[redacted]	
Appendix B Blood Sampling Volume Tables	• PK sampling time point blood draws added 1-2 hours after the EOI [redacted] • Total amount of blood drawn per time point adjusted [redacted]; total amount of blood drawn per 12-month study period adjusted [redacted].

Table 5: Summary of Changes Between Amendment 2 and Amendment 3

Section	Description of Change
Cover page	• Protocol title updated to reflect addition of infants and children to the study population. (This change has been carried through to all other locations in which the protocol title is shown.) • Updated responsible study personnel.
Sponsor Signature Page	• Updated responsible medical officer. • Added additional signatories.
Procedures in Case of Emergency	Updated contact information for reporting SAEs.
2 Synopsis	• The study period has been adjusted to accommodate long-term follow-up until approval or decision reached on further development of ORGN001, and last patient completion date has been adjusted to 4Q2022. • The study background/ rationale, study objectives, endpoints, methodology, inclusion/exclusion criteria, and statistical methods have been updated to reflect the changes detailed in sections below that have been made to expand the study subject population to include older infants and children with MoCD.
2.1 Background	The background has been revised to include information on older children and infants with MoCD.
2.2 Rationale for the Study	Additional text: "Responsibility for the development of ORGN001 in the treatment of MoCD Type A was assumed by Origin Biosciences, Inc, in September 2018."
2.3 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."

Section	Description of Change
2.4 Rationale for Patient Population	Additional text: • "However, the clinical presentation after the neonatal period appears to be more heterogeneous and may progress less rapidly in some patients. In an effort to more fully characterize the potential impact of ORGN001 in MoCD Type A, the study has thus been modified to include infants and children with MoCD Type A, who are treatment-naïve or may have previously received ORGN001 through the early access program (EAP). Infants are defined as those from 29 days to <2 years of age in Amendment 3. Children are defined as those from 2 to 5 years of age (inclusive)." • "In infants or children, eligibility will be determined by confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A."
2.5 Rationale for Proposed Dosing	Additional text and tables have been added on the basis of a population PK (PopPK) model: • "Since then, higher doses have been studied and were all well tolerated in rats and dogs using an improved IV formulation. Accordingly, the revised NOAEL values in a [redacted] rat study provide a considerable increase in the safety margins [redacted]." • "The dosing strategy in Table 9 has been simplified compared to the original guidance. This is justified given 1) the much greater safety margin with respect to the NOAEL in the [redacted] rat study described above; 2) the excellent safety profile of ORGN001 thus far with all patients tolerating the maximum 1200 µg/kg/day dose and no safety signals identified [redacted]; and 3) the fact that dose increments [redacted] were well tolerated in Study ALXN1101-MCD-201."
2.6 Rationale for Overall Study Design	Additional text: "Less frequently, older infants and children may present with neurologic symptoms related to MoCD such as seizures, movement disorder, and developmental delay/disability that appears to have a less rapidly evolving course."
3.1 Objectives	• Primary objective updated to include infants and pediatric patients who are either treatment-naïve or who have received compassionate use ORGN001. • Secondary objectives updated to encompass evaluation of [redacted] the effect of ORGN001 on growth and development using age-appropriate assessments, [redacted]

Section	Description of Change
3.2 Endpoints	Primary efficacy endpoint modified to overall survival. Secondary efficacy endpoints modified to include variables (eg, changes in growth parameters, feeding pattern assessments, and developmental assessments) appropriate to the expanded study subject population and study period. [redacted]
4.1 Overall Study Design	Additional text: • "Infants are defined as those from 29 days to < 2 years. Children are defined as those from 2 years to 5 years (inclusive) at the time of informed consent." • [redacted] • "Eligible patients beyond the neonatal period with genetically confirmed evidence of MoCD Type A, a biochemical profile, and clinical picture consistent with MoCD Type may also be enrolled following completion of Screening/Baseline assessments." • "Data from procedures conducted as part of standard of care prior to study participation may be collected as part of Medical History. Genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases." • "Due to the rare nature of the disease and no currently available treatment, patients exceeding 36 months of treatment may continue to receive study drug until ORGN001 becomes commercially available or development has stopped. For patients receiving ORGN001 [redacted] a safety visit will occur [redacted]. Assessments performed during those visits are for the purposes of ongoing safety to receive ORGN001 and may only occur if ORGN001 is not yet commercially available for the patient." • [redacted]
4.2 Number of Patients	Revised so that no minimum or maximum number of patients is projected for enrollment in the study.

Section	Description of Change
4.3 Study Assessments	• Updated to include any differences in assessment between neonates, infants, and children [redacted] • Vital signs assessment [redacted] specified as predose (Section 4.3.6). Additional systolic and diastolic blood pressure measurements to be collected [redacted] 30 minutes post-EOI was added as a time point. • Serum osmolality added as a parameter of blood chemistry/hematology sample analysis to align with the assessment table and CRF (Section 4.3.8). • Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) added as an alternative to the Bayley-III for those patients developmentally beyond the Bayley-III (Section 4.3.12).
5 Schedules of Assessments: (Screening/Baseline and 12-Month Study Period)	• [redacted]. • WPPSI-IV listed as alternative to the Bayley-III. • [redacted] • Brain ultrasound specified for neonates only. • Footnote added that additional systolic and diastolic blood pressure measurements are to be collected [redacted] at approximately 30, 60, 90, and 120 minutes post-EOI and at 6 and 12 hours post-EOI.
5 Schedules of Assessments: (Long-Term Treatment Period and Safety Follow Up)	• WPPSI-IV listed as alternative to the Bayley-III. • Safety Follow-up ET Visit column has had developmental assessments added as included and a footnote made stating that these assessments will only occur [redacted] for children continuing on ORGN001 past the study follow up period where ORGN001 is not commercially available.
5 Schedules of Assessments: (Following Recommendation by the Safety Review Committee for an Unscheduled Dose Adjustment)	• PD blood sampling to occur predose. • PK blood sampling to occur at EOI (±5 minutes), 1 to 2 hours after the EOI, and 3 to 4 hours after the EOI.
6.3 Definition of Study End	Additional text: "Due to the rare nature of the disease and no currently available treatment, patients exceeding 36 months of treatment may continue to receive study drug until ORGN001 becomes commercially available or development has stopped."

Section	Description of Change
7.2 Patient Inclusion Criteria	Additional text for the first criterion: "or infant (29 days to < 2 years of age) or child (2 to 5 years of age [inclusive]) with MoCD Type A, previously untreated with ORGN001 or treated with ORGN001 through the EAP" Additional criterion added: • In infants or children, diagnosis of MoCD Type A, based on: – Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A
[redacted]	[redacted]
[redacted]	[redacted]
10 Pharmacodynamics Assessments	Timing of additional blood and urine sample collection following unscheduled dose adjustments changed to be as follows: On the first day the adjusted dose is administered, the patient will be administered study drug in-clinic, and a pre-dose blood sample will be collected on the first day of the dose adjustment [redacted]. A urine sample will be collected at any time during [redacted] the dose adjustment visit.
11 Pharmacokinetics Assessments	[redacted] • An additional PK sample was added to occur at 1 to 2 hours after EOI on regularly scheduled collection days, [redacted] or on the first day of an unscheduled dose adjustment.
[redacted]	[redacted]
14 Statistical Methods and Planned Analyses	Added text: • "Assessments will be binned into analysis visits in such a way that the assessment closest to the target study day among all assessments observed within a window around the target day will be designated for analyses over time. [redacted] • "Continuous variables will be summarized using mean, SD, median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency distributions. Confidence intervals will be provided for all means and percentages to aid in interpretation."
14.1 Determination of Sample Size	Previous section contents deleted; revised to read as follows:

Section	Description of Change
	"There will be no minimum or maximum number of patients for this study. The final sample size and determination of study success relative to efficacy will depend on the overall survival rate as each successive patient reaches study completion."
14.2 Analysis Populations	A Full Analysis Set (FAS) has been defined for performance of the efficacy analyses; the FAS is defined as patients with a confirmed diagnosis of MoCD Type A who have no antenatal and/or postnatal brain imaging prior to initiation of treatment with ORGN001 that indicates cortical or subcortical cystic encephalomalacia or clinically significant intracranial hemorrhage. Additional text: "Additionally, two modified Full Analysis Sets (mFAS) will be used to support the analyses on the FAS: • Neonate mFAS (NmFAS), [redacted] • Pediatric mFAS (PmFAS), [redacted]"
14.3 Efficacy and Pharmacokinetic Endpoints	**Primary Efficacy Endpoint:** Changed to be overall survival. [redacted] • Changes in growth parameters (height, weight, BMI, head circumference) through Month 12 • Feeding pattern assessments through Month 12 • GMFCS-E&R results through Month 12 • GMFM-88 results through Month 12 [redacted]

Section	Description of Change
	[redacted]
14.4 Demographics and Baseline Characteristics	Fas, NmFAS, and PmFAS added.
14.5 Patient Disposition and Extent of Exposure	Text added: "The number of patients screened, treated, continuing treatment after confirmation of enrollment criteria, and completing the 12-month and 36-month study periods will be tabulated. Reasons for any patient withdrawals will be provided. The number of patients in the safety and efficacy analysis sets, along with reasons for exclusion from analysis sets, will be tabulated."
14.7 Efficacy Analyses	Fas, NmFAS, and PmFAS added.
14.7.1 Use of Natural History Study ALX-MCD-502	Entire section new (compared to Amendment 2)
14.7.2 Primary Efficacy Analysis	[redacted] "The primary efficacy analysis will summarize overall survival, defined as the interval in months from the date of birth to the date of death or date last known alive (patients still on study will be censored at the data cutoff date), whichever occurs first. The analysis of OS will be based on the Kaplan-Meier methodology for estimation of survival parameters. The median duration of OS will be estimated based on the 50th percentile of the Kaplan-Meier distribution; additional summary statistics, including the 25th and 75th percentiles, 95% confidence intervals (CIs) on the median and the other percentiles and proportion of censored patients. The analysis of OS will be done using the FAS, the NmFAS, and the PmFAS."
14.7.3 Secondary Efficacy Analyses	[redacted]

Section	Description of Change
	Text added: • "Body weight, length, head circumference, and BMI will be analyzed by converting each parameter to age-adjusted z-scores and age percentiles, and descriptive statistics will be presented to each parameter through Month 12." • "Changes in motor function through Month 12 will be summarized based on data from the administration of the GMFCS-E&R, which is a 5-level classification system that classifies gross motor functional capabilities and limitations as usual performance in the home, school, and community setting." • "The Bayley-III Cognitive and Motor scaled scores and composite scores, as well as percentile ranks, and age equivalents will be summarized through Month 12. Where appropriate, the WPPSI-IV will be used instead of the Bayley-III." • "PEDI standard and scaled scores will be summarized by self-care, mobility, and social function domains through Month 12."
[redacted]	[redacted]
[redacted]	
14.8.1 Adverse Events	Text added: "Summaries will include both the number of patients affected and the number of events. For patient counts in summaries by severity or relationship, 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 in the most extreme category of severity or relationship observed."
Appendix B Blood Sampling Volume Tables	Modifications made herein to match time points from the Schedules of Assessments and elsewhere changed within the document:

Section	Description of Change
	• PK sampling time point blood draws added 1-2 hours after the EOI [redacted] • Total amount of blood drawn per time point adjusted [redacted]; total amount of blood drawn per 12-month study period adjusted [redacted].

Table 6: Summary of Changes Between Amendment 3 and Amendment 4

Section	Description of Change
Administrative	Updates to table numbers throughout the protocol to account for additional summary of changes table for protocol amendment 4
[redacted]	[redacted]
4.3.7	Electrocardiograms will be collected for each patient at Screening/Baseline when feasible, [redacted] and at any Safety Follow-up Visit, and at the Early Termination Visit, if applicable, or as per SRC recommendation.
4.3.8	[redacted] If the PK collection kit is not received in time for PK sample collection on Day 1, PK samples may be drawn any time [redacted] PK samples should be collected at EOI (±5 minutes), 1 to 2 hours after EOI, and 3 to 4 hours after EOI. **If the sample is collected on Day 1, a pre-dose sample should also be collected.**
5. Table 10 [redacted], Schedule of Assessments	Addition of pre-dose pharmacokinetic sampling to footnote "o": • Pharmacokinetic sampling will be conducted at the EOI ±5 minutes, 1 to 2 hours after EOI, and 3 to 4 hours after EOI [redacted]. **On Day 1 only a pre-dose sample will also be collected.** [redacted] Addition of time point 30 minutes has been added to footnote "c":

Section	Description of Change
	• [redacted] additional systolic and diastolic blood pressure measurements are to be collected at approximately **30**, 60, 90, and 120 minutes post- EOI, and at 6 and 12 hours post-EOI.
5. Table 12 [redacted]: Schedule of Assessments (Following Recommendation by the Safety Review Committee for an Unscheduled Dose Adjustment)	To match protocol language, addition of tick box for urinalysis on *First Day Adjusted Dose is Administered*.
10. Pharmacodynamic Assessments	The PD blood draw volume for the safety follow up visit was updated: • At any Safety Follow-up Visit, a PD blood sample [redacted] will be collected.
11. Pharmacokinetic Assessments	Addition of pre-dose pharmacokinetic sampling: [redacted] ○ ***Pre-dose at Day 1 only*** ○ *at the EOI ±5 minutes* ○ *1 to 2 hours after EOI* ○ *3 to 4 hours after EOI* Clarification to language in the following section: Following recommendation by the SRC for an unscheduled dose adjustment, blood samples will be collected for assessment of PK parameters, as follows: 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), 1 to 2 hours after the EOI, and at 3 to 4 hours after the EOI. The time of infusion, PK sample collection, the dose administered, and the start and stop time of IV infusion are to be recorded in the CRF. [redacted] **following an unscheduled dose adjustment, a PK sample will be collected at 1 to 2 hours after EOI.**
Appendix B, Blood Sampling Volumes Tables; Table 15 [redacted]: Blood Sampling Volumes (in mL) During the 12-Month Study Period	• Addition of pre-dose pharmacokinetic sampling on Day 1 ○ Update to blood volumes in table to account for pre-dose sample collection [redacted] (planned dose-escalation visits)
Appendix B, Blood Sampling Volumes Table 16 [redacted]: Blood Sampling Volumes During the Long-Term Extension Period, After a Dose Adjustment, and at the Safety Follow-up	• Update to [redacted] account for pre-dose sample collection on unscheduled dose adjustment and safety follow up visits.

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Table 7: Abbreviations and Special Terms

Abbreviation	Definition
AE	Adverse event
Alexion	Alexion Pharma GmbH (former Sponsor)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
Bayley-III	Bayley Scales of Infant Development-Third Edition
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
Colbourne	Colbourne Pharmaceuticals GmbH
cPMP	Cyclic pyranopterin monophosphate
CRF	Case Report Form (paper or electronic)
CSR	Clinical study report
CYP 450	Cytochrome P450
DMC	Data Monitoring Committee
DWI	Diffusion-weighted imaging
EC	Ethics Committee
ECG	Electrocardiogram
E. coli	*Escherichia coli*
EDC	Electronic data capture
EEG	Electroencephalogram
EOI	End-of-infusion
GA	Gestational age
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GLP	Good Laboratory Practice
GMFCS-E&R	Gross Motor Function Classification System Expanded and Revised
GMFM-88	Gross Motor Function Measure – 88
GTP	Guanosine triphosphate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IV	Intravenous(ly)
JP	Japanese Pharmacopeia
LC-MS/MS	Liquid chromatography with tandem mass spectrometric detection
mFAS	Modified Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
MoCD	Molybdenum cofactor deficiency
MoCo	Molybdenum cofactor
MRI	Magnetic resonance imaging
NOAEL	No observable adverse effect level
Origin	Origin Biosciences, Inc. (Sponsor)
OPC	Objective performance criterion
OS	Overall survival
PD	Pharmacodynamic(s)
PEDI	Pediatric Evaluation of Disability Inventory

Abbreviation	Definition
Ph Eur	European Pharmacopoeia
PK	Pharmacokinetic(s)
PopPK	Population PK
Q.S.	Quantity sufficient
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
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopeia
WHODrug	World Health Organization Drug Dictionary
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition

2. INTRODUCTION

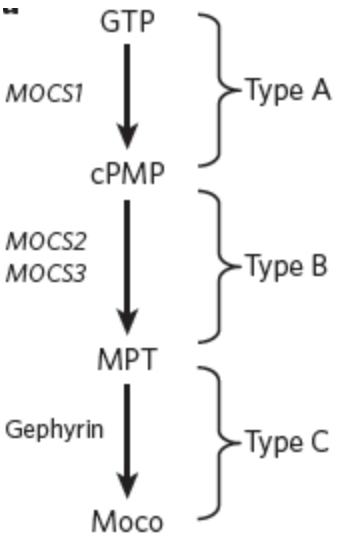
2.1. Background

Molybdenum cofactor deficiency (MoCD) is a rare, life-threatening, autosomal recessive, inborn error of metabolism that is characterized by disruption of the metabolic pathway for production of molybdenum cofactor (MoCo). Molybdenum cofactor is essential for functioning of the enzymes sulphite oxidase (SO), xanthine oxidoreductase, and aldehyde oxidase activity (Schwarz 2009). The loss of SO activity is responsible for the severe and rapidly progressive neurologic damage seen in neonates presenting with MoCD (Reiss 2003; Schwarz 2009). Less frequently, older infants and children may present with neurologic symptoms related to MoCD such as seizures, movement disorder, and developmental delay/disability that appears to have a less rapidly evolving course.

Although there are three types of MoCD, two-thirds of MoCD patients have Type A, which is due to a mutation in the *MOCS1* gene localized on chromosome 6p21.2. In MoCD Type A, the first of four synthetic steps in the formation of molybdenum cofactor is interrupted, and guanosine triphosphate (GTP) cannot be converted into cyclic pyranopterin monophosphate (cPMP). Diagnosis of MoCD Type A in neonates is based on clinical and laboratory presentation (eg, seizures, exaggerated startle response, high-pitched cry, intracranial hemorrhage, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or S-sulfocysteine [SSC], or low or absent uric acid in the urine or blood) and is then confirmed by genetic testing. The clinical presentation after the neonatal period appears to be more heterogeneous and may progress less rapidly.

The biosynthetic pathway for MoCo synthesis involves 3 major steps; see Figure 1 (Schwarz 2009).

Figure 1: The Metabolic Pathway for Molybdenum Cofactor



The incidence of MoCD is estimated to be between 1/100,000 and 1/200,000 newborn babies worldwide (Schwahn 2015). Affected individuals with MoCD Type A usually present as

neonates with severe symptoms that are observed as part of standard clinical practice. These include, but are not limited to, intractable seizures, burst-suppression on multifocal epileptic encephalogram, exaggerated startle reactions, axial hypotonia, limb hypertonia, and feeding difficulties (Van der Knaap 2005; Johnson 2001; Vijayakumar 2011). Death commonly occurs in the neonatal period and patients who survive that period may develop a severe static encephalopathy and developmental delays due to central nervous system (CNS) injury, including subcortical cystic cavitation, hydrocephalus, diffuse cortical atrophy, and basal ganglia injury.

2.1.1. Treatment Options for MoCD Type A

There is no available approved treatment for MoCD Type A. Current management strategies are symptomatic and aim to provide relief from MoCD Type A clinical manifestations as well as to provide palliative care. Administration of a diet with restrictions on the sulfur-containing amino acids cysteine, methionine, and taurine has been attempted in the related disorder of SO deficiency (Touati 2000).

2.2. Rationale for the Study

The previous Sponsor, Alexion Pharma GmbH (Alexion) developed ORGN001 (formerly known as ALXN1101), a synthetic form of cPMP and a precursor molecule to MoCo, as a treatment for MoCD Type A. Responsibility for the development of ORGN001 in the treatment of MoCD Type A was assumed by Origin Biosciences, Inc, in September 2018. ORGN001 provides a therapeutic approach for the treatment of MoCD Type A that is intended to restore MoCo biosynthesis. Results from nonclinical pharmacology studies with ORGN001 suggest that the metabolic abnormality in MoCD Type A could be corrected by administration of synthetic cPMP, resulting in restoration of enzymatic activity and correction of the metabolic pathways that lead to accumulation of toxic metabolites that cause CNS injury.

A comprehensive nonclinical package, including proof-of-concept in a knock-out mouse model, *in vitro* and *in vivo* safety pharmacology and pharmacokinetic (PK) studies (in rats and dogs), cytochrome inhibition/induction, metabolism characterization, and transporter profiling in various species, and a standard battery of toxicology studies *in vitro* and *in vivo* (rats and dogs), has been generated to support the clinical use of ORGN001. Two additional Good Laboratory Practice (GLP)-compliant toxicity studies in juvenile animals [redacted] have been performed to support the use of ORGN001 in the target patient population. [redacted]

The use of ORGN001 as a potential treatment for MoCD Type A is supported by preliminary clinical evidence obtained from pediatric patients with MoCD treated with a recombinant *Escherichia coli*-derived cPMP product (rcPMP) from Colbourne Pharmaceuticals GmbH (Colbourne; formerly known as Orphatec Pharmaceuticals GmbH) [redacted]. Published individual case reports suggest that intravenous (IV) administration of rcPMP may restore MoCo-dependent enzyme activities, as evidenced by reduction in the concentrations of disease biomarkers. Elevated urinary SSC concentrations observed before initiation of treatment were corrected with rcPMP substitution. Recombinant *E.coli*-derived cPMP substitution also resulted in improved

neurologic outcomes for patients with MoCD Type A (Veldman 2010a; Hitzert 2012a). Safety data from published literature describing these patients has indicated that rcPMP infusions were well tolerated (Veldman 2010a; Hitzert 2012a).

Schwahn and colleagues reported on an observational, prospective cohort study of 16 neonates diagnosed with MoCD (11 Type A and 5 Type B) for up to 5 years that included patients reported by Veldman and Hitzert (Schwahn 2015; Hitzert 2012a; Veldman 2010b; Veldman 2010a; Veldman 2010a; Veldman 2010a). Rapid, near-normalization of urinary biomarkers occurred within 2 days of rcPMP treatment but was only observed in patients with Type A disease. Biomarker response was maintained for up to 5 years on continued rcPMP treatment. Moreover, patients exhibited clinical responses; seizure activity observed in 9 of 11 patients with MoCD Type A was either completely suppressed or substantially reduced following administration of rcPMP. Clinical deterioration was reported to have stopped upon starting rcPMP in 8 patients. Three patients with MoCD Type A that were treated with rcPMP prior to the onset of severe encephalopathy did not develop clinically significant disability. Their initial magnetic resonance imaging (MRI) scans demonstrated no signs of necrosis or cystic lesions. After 2 to 4 years of cPMP treatment, their MRI scans were normal or demonstrated minimal atrophy and hypomyelination. These 3 patients remained seizure free and progressed towards developmental milestones. Notably, 2 of these 3 patients were suspected to have MoCD prenatally, and all started rcPMP supplementation within 7 days from the onset of symptoms, emphasizing the importance of early initiation of treatment with cPMP. Additionally, the disparity in between the number of patients with MoCD Type A who experienced near normalization of biomarkers compared with those who did not develop clinically significant disability on rcPMP illustrate how the acute and profound neurotoxicity associated with MoCD leaves a narrow treatment window whereby cPMP supplementation may prevent irreversible damage. Given that some of the neurotoxicity occurs in utero, it is perhaps unsurprising that prenatal diagnosis, early inducement of labor, and prompt treatment with cPMP have been associated with favorable outcomes (Schwahn 2015; Hitzert 2012b).

Considering the identical molecular structures of ORGN001 and rcPMP, and the clinical results reported with rcPMP, it is anticipated that treatment with ORGN001 will benefit patients with MoCD Type A in Study ALXN1101-MCD-202 by reconstituting MoCo synthesis, restoring SO enzymatic activity, and resulting in reduced concentrations of toxic metabolites (sulfite and SSC).

2.3. Risk/Benefit Assessment

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 is common in the neonatal period, with a median survival of patients with MoCD of 3 years (Mechler 2015). Currently, no approved therapy is available for the treatment of patients with MoCD Type A. Treatment strategies for individuals with this disorder are symptomatic and with a goal to provide relief from clinical disease manifestations and along with palliative care for the patient.

Safety data from the completed Study ALXN1101-MCD-101 in healthy adult volunteers and the ongoing Study ALXN1101-MCD-201 in patients with MoCD Type A support the study of ORGN001 as a treatment for MoCD Type A. [redacted] healthy volunteers received ORGN001 in the Phase 1 first-in-human study, ALXN1101-MCD-101, in which ORGN001 was well-tolerated

at doses [redacted] administered IV. [redacted] Across both cohorts, no deaths or life-threatening TEAEs occurred, and no patient had to withdraw due to a TEAE.

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.

An ongoing Phase 2 study, ALXN1101-MCD-201, is designed to transition patients with MoCD Type A from the recombinant form of cPMP produced by Colbourne to ORGN001. [redacted] To date, ORGN001 has been well-tolerated, and there have been no serious adverse reactions with causality attributed to ORGN001 reported, and no patient has withdrawn or discontinued as a result of an adverse event (AE).

Due to the life-threatening and debilitating nature of the disease, lack of treatment, and shortened life expectancy of these patients, there is a significant need to provide safe and effective treatment for patients with MoCD Type A. A treatment paradigm that targets the underlying cause of the disease, the inability to synthesize MoCo from its precursor, GTP, may restore MoCo biosynthesis and SO function, and ameliorate MoCD disease progression.

2.4. Rationale for Patient Population

Preliminary data suggest that the metabolic derangement of MoCD starts in utero and patients demonstrate symptoms associated with sulfite toxicity within hours of birth (Veldman 2010a; Hitzert 2012a). This observation supports the premise that irreversible neurologic injury may occur very early in life and that immediate postnatal treatment with ORGN001 may alter the outcome of this devastating disorder.

Selection of the patient population to determine ORGN001 efficacy and safety in Study ALXN1101-MCD-202 was based on the population that is most likely to benefit from ORGN001 treatment. Considerations were given to the age of onset of the disease and the extent of CNS injury at time of diagnosis and/or planned treatment. Consequently, the population initially identified to be enrolled in Study ALXN1101-MCD-202 comprised patients from 1 to 28 days of age (inclusive) at the time of first ORGN001 dose administration (neonates), with Day 1 of age corresponding to the day of birth. However, the clinical presentation after the neonatal period appears to be more heterogeneous and may progress less rapidly in some patients. In an effort to more fully characterize the potential impact of ORGN001 in MoCD Type A, the study has thus been modified to include infants and children with MoCD Type A, who are treatment-naïve or may have previously received ORGN001 through the early access program (EAP). Infants are defined as those from 29 days to <2 years of age. Children are defined as those from 2 to 5 years of age (inclusive). In neonates, eligibility will be determined by prenatal genetic diagnosis of MoCD Type A or presence of signs and symptoms consistent with the diagnosis of MoCD Type A. Genetic testing will be performed to confirm the MoCD Type A

genotype. In infants or children, eligibility will be determined by confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A.

2.5. Rationale for Proposed Dosing

A population PK (PopPK)-based approach has been utilized to create a dosing scheme that targets the higher end of the originally acceptable exposure range for ORGN001 (NOAEL: area under the plasma concentration-time curve [redacted]) at the highest dose studied in the original toxicology study that was limited by solubility issues. Since then, higher doses have been studied and were all well tolerated in rats and dogs using an improved IV formulation. Accordingly, the revised NOAEL values in a [redacted] rat study provide a considerable increase in the safety margins [redacted].

[redacted]

A PopPK model was derived to characterize ORGN001 clinical PK in healthy adult volunteers (Study ALXN1101-MCD-101) and children with MoCD Type A (Study ALXN1101-MCD-201). Due to [redacted] renal clearance of ORGN001 in adults (Study ALXN1101-MCD-101), a function was included to account for the expected impact of renal function maturation (Rhodin 2009) on ORGN001 PK in neonate patients. [redacted]

Dosing will be based upon the gestational age (GA) of the patient. Day 1 dosing for term (≥ 37 weeks GA) and preterm neonate (< 37 weeks GA) patients will begin with ORGN001 IV infusions of 700 and 525 µg/kg/day, respectively. Following Investigator and Safety Review Committee (SRC) reviews (as well as Data Monitoring Committee [DMC] review of data prior to the first dose adjustment for each patient as well as subsequent periodic review of cumulative data), recommended dosing may follow the guidance in Table 9.

The dosing strategy in Table 9 has been simplified compared to the original guidance. This is justified given 1) the much greater safety margin with respect to the NOAEL in the [redacted] rat

study described above; 2) the excellent safety profile of ORGN001 thus far with all patients tolerating the maximum 1200 µg/kg/day dose and no safety signals identified [redacted]; and 3) the fact that dose increments [redacted] were well tolerated in Study ALXN1101-MCD-201.

Table 9: Dosing and Dose Adjustment for Term and Preterm Neonate Patients, Older Infants, and Children in Study ALXN1101-MCD-202

Study Day	Term Neonate (GA ≥ 37 weeks) and Older Infants/Children Dose (µg/kg/day)	Preterm Neonate (GA < 37 weeks) Dose (µg/kg/day)
Day 1	700	525
Day 28	1000	900
Month 3	1200	1200

Abbreviations: GA = gestational age.

Doses may be adjusted based on drug-related AEs or changes in clinical parameters, laboratory data, or PK findings and will occur following consultation with the medical monitor and, if applicable, with the SRC.

[redacted]

ORGN001 drug product has been developed for IV use. Administration via the parenteral route results in rapid and consistent onset of action necessary for treatment of neonatal patients with MoCD. The dose can be adapted to the last recorded body weight or body weights recorded by the home care giver and/or physician visits with appropriate documentation; the flexibility to adjust doses based on changes in body weight enable accurate dosing.

2.6. Rationale for the Overall Design

This is a Phase 2/3 open-label, multicenter study to assess the safety and efficacy of ORGN001 in neonates, infants, and children with MoCD Type A.

A placebo-controlled study is not feasible or ethical due to the severity of the untreated disease and reports of improved outcomes in MoCD Type A neonates treated with rcPMP; also, the lack of available treatment precludes inclusion of an active control arm. ORGN001 safety will be reviewed continuously, on an individual patient basis, as well as at a group level. An SRC, [redacted] will review all available safety, efficacy and PK data on a periodic basis.

In neonate patients with signs and symptoms consistent with MoCD Type A, treatment should be initiated as soon as feasible, in an effort to prevent the irreversible neurologic damage that is expected to occur. Less frequently, older infants and children may present with neurologic

symptoms related to MoCD such as seizures, movement disorder, and developmental delay/disability that appears to have a less rapidly evolving course.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

Primary:

- To evaluate the safety and efficacy of ORGN001 in neonate, infant, and pediatric patients with MoCD Type A who are either treatment-naïve or who have received compassionate use ORGN001

Secondary:

- [redacted]
- To evaluate the effect of ORGN001 on growth and development using age-appropriate assessments
- To evaluate the effect of ORGN001 on pediatric measures of functional ability and activities of daily living
- [redacted]

[redacted]

- [redacted]
- [redacted]

3.2. Endpoints

Primary Efficacy Endpoint:

- Overall survival (OS)

Secondary Efficacy Endpoints:

- [redacted]
- Changes in growth parameters (height, weight, body mass index (BMI), head circumference) through Month 12
- Feeding pattern assessments through Month 12
- Gross Motor Function Classification System Expanded and Revised (GMFCS-E&R) results through Month 12
- Assessments of the Bayley Scales of Infant Development – Third Edition (Bayley-III) Cognitive and Motor Scales as measured through Month 12

  - For children aged 3 and above, for whom the Bayley-III is no longer appropriate, the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) will be administered.
  - For patients with severe developmental delay, the WPPSI may not be an appropriate assessment, and therefore, the Bayley-III may be administered instead.

- Functional ability and activities of daily living, measured by the Pediatric Evaluation of Disability Inventory (PEDI) through Month 12
- Gross Motor Function Measure (GMFM)-88 results through Month 12

[redacted]

[redacted]

Safety Endpoints:

- The type, frequency, severity, timing, and relationship to study drug of any AEs, serious AEs (SAEs), and changes in vital signs, electrocardiograms, and safety laboratory tests

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This Phase 2/3, multicenter, multinational, open-label study is designed to evaluate the efficacy and safety of daily IV administration of ORGN001 to neonates, infants, and children with MoCD Type A. For the purposes of this study, neonate patients are defined as those from 1 to 28 days of age (inclusive) at the time of first ORGN001 administration, with day 1 of age corresponding to the day of birth. Infants are defined as those from 29 days to < 2 years. Children are defined as those from 2 years to 5 years (inclusive) at the time of informed consent.

Eligible neonates with a prenatal diagnosis of MoCD Type A will undergo Screening/Baseline assessments (eg, brain imaging) prior to or as soon as possible after birth and prior to receiving the first IV infusion of ORGN001. Given the life-threatening and devastating nature of the disease and the potential for a favorable benefit:risk profile for treatment with ORGN001, patients with a prenatal diagnosis may be treated prior to the onset of signs and symptoms associated with MoCD Type A. Additionally, if it is not possible to obtain brain imaging prior to treatment, the priority would be to treat the neonate and obtain brain imaging as soon as feasible afterwards. For those patients, the patient's legal guardians (per country-specific requirements) may be asked to provide informed consent for participation in the study prior to delivery. [redacted]

Eligible neonates who do not have a prenatal diagnosis of MoCD Type A but who have the onset of signs and symptoms that may serve as the basis for diagnosis will undergo Screening/Baseline assessments as soon as possible prior to receiving their first daily IV infusion of ORGN001. Data from procedures conducted as part of standard of care prior to study participation may be collected as part of Medical History. Genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy.

Eligible patients beyond the neonatal period with genetically confirmed evidence of MoCD Type A, a biochemical profile, and clinical picture consistent with MoCD Type may also be enrolled following completion of Screening/Baseline assessments. Data from procedures conducted as part of standard of care prior to study participation may be collected as part of Medical History. Genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases.

This study will include a Screening Period, a 12-month Study Period, and a 2-year long-term Treatment Period (Months 13 through 36). Due to the rare nature of the disease and no currently available treatment, patients [redacted] may continue to receive study drug until ORGN001 becomes commercially available or development has stopped. For patients receiving ORGN001 past month 36, a safety visit will occur [redacted]. Assessments performed during those visits are for the purposes of ongoing safety to receive ORGN001 and may only occur if ORGN001 is not yet commercially available for the patient.

The study will enroll both term and preterm neonates as well as infants and children who meet inclusion and exclusion criteria. In neonates, due to the roles that renal clearance and body weight play in the PK of ORGN001, dosing will be based upon the GA of the patient. Day 1 dosing for term (≥ 37 weeks GA) and preterm neonate (< 37 weeks GA) patients will begin with

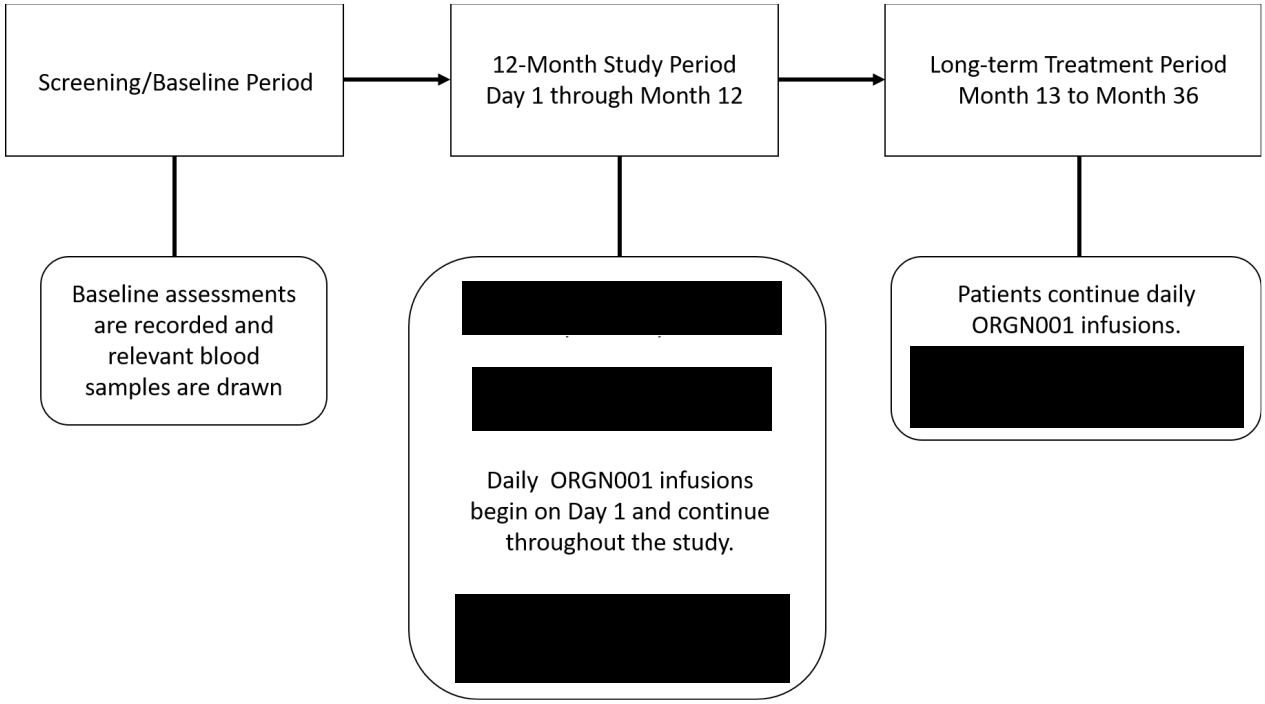
ORGN001 IV infusions of 700 µg/kg/day and 525 µg/kg/day, respectively. ORGN001 infusions should be administered every 24 hours ± 3 hours apart while hospitalized or at home.

Based on the Investigator and SRC/DMC review of all available data prior to the first (Day 28) dose adjustment, each patient's dose may be initially escalated on or before Day 28, with incremental adjustments up to 1200 µg/kg/day by Month 3. Post administration of the increased dose, patients will undergo an electrocardiogram (ECG) as well as PK sampling. If any dose is not tolerated, the dose will be reduced based on an ad hoc consultation with the SRC/DMC (also see Section 6.1.2 for rules on stopping or delaying dosing).

[redacted] patients will [redacted] to receive daily infusions of ORGN001 [redacted] and will return to the clinic for study visits to assess safety, efficacy, and PK.

Every effort will be made to prevent or, if unavoidable, minimize pain that may occur in association with 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, for whom less blood volume should be collected, must be used [redacted]

Figure 2: Study Design for Study ALXN1101-MCD-202[a]



[a] Patients who reach 36 months of treatment may continue to receive study drug until ORGN001 becomes commercially available or development has stopped. [redacted]

4.2. Number of Patients

No minimum or maximum number of patients is projected for enrollment in the study.

4.3. Study Assessments

No study procedures may be performed prior to obtaining informed consent. Screening/Baseline and Day 1 assessments may all occur on the same day.

For neonates born prior to 37 weeks of gestation, the Month 12 assessments will be performed at the target time point, adjusted for prematurity by scheduling the visit date plus the addition of the difference between gestational age and full-term gestation of 40 weeks.

Results of all study assessments will be recorded in the appropriate case report form (CRF). Analyses of study assessments are described in Section 14.

4.3.1. Demographic Data

At Screening/Baseline, the patient's date of birth, gender, gestational age, race, and ethnicity will be recorded. The date of first recognition of MoCD-associated signs or symptoms will be documented, as available.

4.3.2. Genotype Assessment

MoCD-related genotype data will be recorded at Screening/Baseline. If not available, a blood sample will be collected for genetic analysis of the *MOCS1* gene. This sample should be collected at Screening/Baseline or as early as possible. Genotype of MoCD Type A will be verified as soon as possible but is not required before dosing is initiated.

4.3.3. Medical History

A complete medical history, including signs and symptoms of MoCD disease, complications during pregnancy, Apgar score, and any history of in-utero seizures, if available, must be recorded at Screening/Baseline for each patient.

4.3.4. Family History

Whether the patient has any siblings (living or deceased) with suspected or confirmed MoCD will be recorded as well as whether the sibling has participated in any other Origin-sponsored studies of MoCD. The degree of parental consanguinity and parental genotypes, if known, should be recorded. Information on parity, delivery type, and placental condition should also be captured. Family history, including the medical history for parents and siblings, will be recorded at Screening/Baseline.

4.3.5. Physical Examination

A physical examination consistent with standard of care must be performed [redacted].

4.3.6. Vital Signs

[redacted] Vital sign assessments will include blood pressure, heart rate, respiratory rate, and temperature.

Additional systolic and diastolic blood pressure measurements are to be collected [redacted] at approximately 30, 60, 90, and 120 minutes post-EOI and at 6 and 12 hours post-EOI.

4.3.7. Electrocardiograms

Electrocardiograms will be collected [redacted] Electrocardiograms should be performed before any blood draws or treatment infusions when those assessments occur at the same study visit.

4.3.8. Laboratory Samples and Assessments

Patients will provide urine samples for assessment of pharmacodynamics (PD) and standard urinalysis. Blood will be collected for blood chemistry, hematology, PK, and PD. Prior to first infusion of ORGN001, if feasible, at least 1 blood sample and 1 urine sample must be collected for PD analysis. This sample collection is essential to establishing whether there are biochemical abnormalities present that are associated with MoCD prior to the initiation of treatment with ORGN001, which would then be expected to rapidly correct those abnormalities for patients with MoCD Type A. Pharmacodynamic blood and urine samples will be evaluated for biomarkers associated with MoCD, including, but not limited to: SSC, [redacted].

Samples will be collected as follows [redacted]

- PD urine [redacted]
- PD blood [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- Blood chemistry and hematology [redacted]
- Standard urinalysis
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- PK [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

If the PK collection kit is not received in time for PK sample collection on Day 1, PK samples may be drawn any time [redacted] PK samples should be collected at EOI (±5 minutes), 1 to 2 hours after EOI, and 3 to 4 hours after EOI. If the sample is collected on Day 1, a pre-dose sample should also be collected.

Capillary blood samples may be collected for analysis of PK, in lieu of venous sampling.

[redacted]

Samples for blood chemistry/hematology should be collected prior to the first ORGN001 infusion on Day 1, if feasible, or may be performed as soon as possible (within 24 hours) after the first infusion. Unless otherwise indicated, if the initial Screening/Baseline sample is not collected until after the first ORGN001 infusion on Day 1, that will be the only blood chemistry/hematology sample collected on Day 1 for the study. Analysis of blood chemistry/hematology samples will include complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, calcium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, serum osmolality, and total serum albumin.

If a dose adjustment is recommended by the SRC/DMC, additional urine or blood samples may be collected for any of the above assessments.

See Appendix A and Appendix B for further details regarding blood sample collection and blood volume limits.

[redacted]

4.3.9. Growth Parameters

Body weight, body length, and head circumference will be recorded at Screening/Baseline and prior to first infusion on Day 1 when feasible; otherwise, these assessments can be performed within 24 hours after first infusion. Measures of growth should also be performed daily [redacted]

4.3.10. Feeding Patterns

Whether the patient is able to feed orally or feeds through a nasogastric or [redacted] feeding tube will be recorded.

This assessment should be performed at Screening/Baseline, prior to first infusion, when feasible, but may be performed within 24 hours after the first infusion. Other feeding pattern assessments should be performed [redacted].

4.3.11. Neurologic Examination and Neuroimaging

A neurologic examination that is consistent with standard of care will be performed [redacted]. The Day 1 assessment must be performed within 2 hours prior to the first infusion. Neurologic examination includes, but is not limited to, spontaneous or abnormal movements, muscle tone, primitive reflexes, and deep tendon reflexes and is part of the physical examination.

For neonate patients, prior to initiation of ORGN001 treatment, a brain ultrasound will be performed in utero and/or after delivery and changes will be assessed over time [redacted].

Brain MRI will be performed [redacted], if available and if clinical conditions allow. Additional scans may be requested, as needed. Completion of a brain MRI may be delayed until after initiation of ORGN001 therapy, if not feasible to complete prior to treatment. [redacted]

4.3.12. Bayley Scales of Infant Development (or Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition)

The Bayley Scales of Infant Development – Third Edition is a standardized and norm-referenced instrument that assesses developmental functioning of infants and children 1 month to 42 months of age; it consists of 5 scales, 3 of which are administered with child interaction by a qualified trained professional: 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 but 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 Bayley-III will be administered [redacted], if applicable to assess changes in gross motor, fine motor, and cognitive development. [redacted]

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

From raw scores, scaled scores and developmental age equivalents can be calculated for the Cognitive, Receptive Communication, 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 (CIs).

A qualified, trained professional will administer the Bayley-III.

Please refer to the Bayley-III Manual for specific definitions of terms and assessments (Bayley 2005).

The WPPSI-IV may be used instead of the Bayley-III depending upon whether the Bayley-III is not appropriate for the patient; similarly, for patients developmentally delayed such that the WPPSI-IV is an inappropriate assessment, the Bayley-III will be used regardless of whether the child is aged 3 or above.

4.3.13. Gross Motor Function Measure–88

Gross motor function will be assessed [redacted], if applicable. Administration of the GMFM-88 must be on the same day/time as the Bayley-III.

The GMFM-88 measures patient-initiated motor activities in 5 dimensions:

- A: Lying and Rolling
- B: Sitting
- C: Crawling and Kneeling
- D: Standing
- E: Walking, Running, and Jumping

Each item is rated from 0 to 3, with 0 equaling “does not initiate,” and 3 equaling “completes item according to all descriptors.” A percent score can be obtained for each dimension, and for the total of all GMFM dimensions. Patients will be assessed without orthoses or aids.

Following scoring of the Bayley-III Gross Motor subtest, items that have duplicate positioning for the GMFM-88 will also be scored. The remaining GMFM-88 items will then be administered

and scored. This is necessary to avoid positional redundancy, fatigue for the infant, and to ensure valid skill measurement of spontaneous gross motor skills.

4.3.14. Gross Motor Function Classification System Expanded and Revised

The GMFCS-E&R will be assessed [redacted], if applicable. [redacted]

The GMFCS-E&R is a 5-level (Level I through Level V) classification system of gross motor function of children and youth (up to 18 years of age), on the basis of 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. The GMFCS-E&R classifies gross motor functional capabilities and limitations as usual performance in the home, school, and community settings.

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" have very little voluntary control of movement, have no means of independent mobility, are generally transported by their caregivers, and require assistance for all activities of daily living.

4.3.15. Pediatric Evaluation of Disability Index

The PEDI measures functional ability and activities of daily living, including self-care, mobility, and social function. The PEDI Functional Skills scales consist of 3 domains:

- Self-Care: Getting Dressed, Keeping Clean, Home Tasks, and Eating and Mealtime
- Mobility: Basic Movement and Transfers, Standing and Walking, Steps and Inclines, Running and Playing, and Wheelchair
- Social: Interaction, Communication, Everyday Cognition, and Self-Management Functional Skills scales

The PEDI will be assessed [redacted], if applicable. [redacted] The PEDI must be performed only after completion of the Bayley-III and the GMFM-88 at those visits where all 3 assessments are administered.

Normative standard scores are available for 21 age groups, based on a child's chronological age, and allow for evaluation of the child's functioning relative to others of the same age. They have a mean of 50, with a standard deviation (SD) of 10. Scaled scores indicate performance along a continuum from 0-100, with increasing numbers representing increased functional performance. Scaled scores provide a means to evaluate a child's current functional skills and progress in these skills over time. Scaled scores are especially helpful in documenting improvements in functional skills for children not expected to exhibit or regain normative levels of functioning.

4.3.16. Ophthalmologic Examination

Ophthalmologic evaluation [redacted] is to include the following:

- Ocular history
- External inspection of the eyes and lids
- Ocular motility assessment
- Pupillary examination
- Red reflex examination
- Age-appropriate visual acuity
- Attempt at ophthalmoscopy

Vision assessment in children younger than 3 years or in any nonverbal child is accomplished by evaluating the child's ability to fix and follow objects. A standard assessment strategy is to determine whether each eye can fixate on an object, maintain fixation, and then follow the object into various gaze positions. Failure to perform these maneuvers indicates significant visual impairment. The assessment should be performed binocularly and then monocularly.

If poor fixation and following is noted, a significant bilateral or unilateral eye or brain abnormality is suspected, and referral for more formal vision assessment is advisable. It is important to ensure that the child is awake and alert because disinterest or poor cooperation can mimic a poor vision response.

Where feasible, visual acuity is documented for each eye in the clinical report form. Also, lens dislocation or subluxation is to be documented separately for each eye if present.

4.3.17. Electroencephalogram and Seizure Activity

Electroencephalograms (EEGs) are to be performed for those patients with documented or suspected seizure activity. Where feasible, a standard EEG [redacted] should be performed prior to the first infusion. If that timing is not possible, the EEG may be performed within 24 hours of initiation of ORGN001 therapy. Subsequent EEGs should be performed in accordance with standard of care.

The [redacted] patient's parent/legal guardian will be given a diary to be used to record data regarding the frequency of seizures and any changes in anticonvulsants for the entire duration of the study.

The patient's parent/legal guardian will be asked at every visit if there has been a presence of seizure activity or any change in seizure activity since the last study visit. Based on a review of the seizure diary as well as observation and review of neurologic examination findings, the Investigator/designee will determine if anticonvulsants, change in medication, or further neuroimaging is warranted.

4.3.18. Vital Status

Vital status will be recorded at specific time points [redacted] to ascertain whether the patient is alive, with respiratory and brain function capable of supporting life.

4.3.19. Concomitant Medications and Procedures

Record any medications that the patient is receiving during the study. Record any nonstudy procedures that the patient undergoes during the study.

4.3.20. Modified Glasgow Coma Scale for Infants and Children

The Glasgow Coma Scale (GCS) is a clinical tool designed to assess coma and impaired consciousness. A modified GCS score of 12 in infants or children suggests a severe head injury, a score of 8 suggests need for intubation and ventilation, and a score of 6 suggests need for intracranial pressure monitoring (see Appendix C). The modified GCS will be administered to patients at every visit, within the first month of the study [redacted].

4.3.21. Follow-up Visits for Patients Who Discontinue

For patients who discontinue ORGN001, Follow-up Visits should be held [redacted] following the last administration of ORGN001. [redacted]

5. SCHEDULES OF ASSESSMENTS

The detailed Schedule of Assessments for the initial 12-month Treatment Period and the Schedule for the long-term Treatment Period are provided [redacted].

Table 10: Schedule of Assessments (Screening/Baseline and 12-Month Study Period)

Assessment	Screening / Baseline	12-Month Study Period
Study Day	[redacted]	
Month		
Visit Window (Days)		
Informed consent		
Eligibility		
Demographic data		
Genotype		
Family history		
Medical history		
Physical examination[b]		
Vital signs[b]		
Vital status		
Additional BP measurements[c]		
Chemistry and Hematology[b,d]		
[redacted]		
Urinalysis[b,e]		
Growth parameters		
Feeding pattern		
Neurologic examination[b]		
Modified Glasgow Coma Scale		
Bayley-III (or WPPSI-IV)[f]		
GMFM-88[g]		
GMFCS-E&R		
PEDI[h]		
Ophthalmologic examination		
Seizure activity[b,i]		

Assessment	Screening / Baseline	12-Month Study Period
Study Day	[redacted]	
Month		
Visit Window (Days)		
Brain MRI[j]		
Brain ultrasound[k] (neonates only)		
ECG[b,l]		
EEG[m]		
PD sampling, urine		
PD sampling, blood[b,n]		
PK sampling[b,o]		
[redacted]		
ORGN001 infusion[p]		**Daily**
Concomitant medications/procedures[b]	X	**Continuous monitoring**
Assess AEs[b]	**Continuous monitoring**	
Follow-up Visits	[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]

With agreement from the Sponsor, some Baseline assessments may be completed after dosing has begun due to urgency of study drug initiation.

[a] For neonate patients born prior to 37 weeks of gestation, the Month 12 assessments will be performed at target time point, adjusted for prematurity by scheduling the visit date plus the addition of the difference between gestational age and full-term gestation of 40 weeks.

[b] These assessments will be performed when any dose adjustment occurs: physical examination, vital signs, neurologic examination, ECG, PD sampling (blood), PK sampling, serum chemistry, hematology, urinalysis, evaluation for seizure activity, assessment of concomitant medications, assessment of AEs. Electrocardiograms should be performed prior to any blood draws or treatment administration scheduled for the same study visits.

[c] [redacted] additional systolic and diastolic blood pressure measurements are to be collected at approximately 30, 60, 90, and 120 minutes post- EOI, and at 6 and 12 hours post-EOI.

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

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

[f] The Bayley-III (or WPPSI-IV, as age-appropriate) may be administered within ± 3 days [redacted].

[g] Administration of the GMFM-88 must be on the same day as the Bayley-III (or WPPSI-IV).

[h] The PEDI must be performed only after completion of the Bayley-III (or WPPSI-IV) and the GMFM-88 at those visits where all 3 assessments are administered

[i] The patient's parent/legal guardian will be given a diary to be used to record data regarding the frequency of seizures and any changes in anticonvulsants for the entire duration of the study. The patient's parent/legal guardian will be asked if there has been a presence of seizure activity or any change in seizure activity since the last study visit. Based on a review of the seizure diary as well as observation and review of neurologic examination findings, the Investigator/designee will determine if anticonvulsants, change in medication, or further neuroimaging is warranted.

[j] Brain MRI should be obtained prior to the first infusion, where feasible. Completion of a brain MRI may be delayed until after initiation of ORGN001 therapy, if not feasible to complete prior to treatment. Brain MRI will be performed for the identified study visits [redacted], if available and if clinical conditions allow. Additional scans may be requested, as needed.

[k] For neonate patients, prior to initiation of ORGN001 treatment, a brain ultrasound will be performed in utero and/or after delivery and changes will be assessed over time (through Day 21) at Screening/Baseline and on Days 3 and 21; see also Section 4.3.11.

[l] Electrocardiograms should be performed prior to any blood draws or treatment administration scheduled for the same study visits. Electrocardiogram at Screening/Baseline, only if feasible.

[m] Perform EEG for patients with documented or suspected seizure activity at Baseline. Where feasible, a standard EEG [redacted] should be performed within 24 hours of first infusion. Subsequent EEGs should be performed in accordance with standard of care.

[n] Pharmacodynamic blood sampling will be conducted predose [redacted].

[o] Pharmacokinetic sampling will be conducted at the EOI ±5 minutes, 1 to 2 hours after EOI, and 3 to 4 hours after EOI [redacted]. On Day 1 only a pre-dose sample will also be collected.

[p] On those days where PK samples are collected, the patient's infusion of ORGN001 must be administered at the study site.

Abbreviations: AEs=adverse events; Bayley-III=Bayley Scales of Infant Development-Third Edition; BP=blood pressure; EEG=electroencephalogram; EOI= end-of-infusion; GMFCS-E&R=Gross Motor Function Classification System Expanded and Revised; GMFM=Gross Motor Function Measure; PD=pharmacodynamics; PEDI=Pediatric Evaluation of Disability Inventory; PK=pharmacokinetics; WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition.

Table 11: Schedule of Assessments (Long-Term Treatment Period and Safety Follow Up)

Assessment	Long-Term Treatment Period				Safety Follow Up/ET Visit[a]
Month	[redacted]				
Visit Window (Days)					
Physical examination					
Vital signs					
Vital status					
Chemistry and Hematology[b]					
Urinalysis[c]					
Growth parameters					
Feeding pattern					
Neurologic examination					
Bayley-III (or WPPSI-IV)[d]					
GMFM-88[e]					
GMFCS-E&R					
PEDI[f]					
Ophthalmologic examination					
Seizure activity[g]					
Brain MRI					
ECG[h]					
PD sampling, urine					
PD sampling, blood[i]					
PK sampling[j]					
ORGN001 infusion[k]	← Daily →				
Assess concomitant medications/procedures	X	X	X	X	X
Assess AEs	X	X	X	X	X

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]

[a] These assessments will only occur every 6 months for children continuing on ORGN001 past the study follow up period where ORGN001 is not commercially available.

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

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

[d] The Bayley-III (or WPPSI-IV, as age-appropriate) may be administered within ± 14 days [redacted].

[e] Administration of the GMFM-88 must be on the same day as the Bayley-III (or WPPSI-IV).

[f] The PEDI must be performed only after completion of the Bayley-III (or WPPSI-IV) and the GMFM-88 at those visits where all 3 assessments are administered.
[g] The patient's parent/legal guardian will be asked if there has been a presence of seizure activity or any change in seizure activity since the last study visit. Based on a review of the seizure diary as well as observation and review of neurologic examination findings, the Investigator/designee will determine if anticonvulsants, change in medication, or further neuroimaging is warranted.
[h] Electrocardiograms should be performed prior to any blood draws scheduled for the same study visits.
[i] Pharmacodynamic blood sampling will be conducted predose [redacted].
[j] Pharmacokinetic sampling will be conducted at the EOI ±5 minutes, 1 to 2 hours after EOI, and 3 to 4 hours after EOI [redacted].
[k] On those days where PK samples are collected, the patient's infusion of ORGN001 must be administered at the study site.
Abbreviations: AEs=adverse events; Bayley-III=Bayley Scales of Infant Development-Third Edition; ECG=electrocardiogram; ET=early termination; GMFCS-E&R=Gross Motor Function Classification System Expanded and Revised; GMFM=Gross Motor Function Measure; MRI=magnetic resonance imaging; PD=pharmacodynamics; PEDI=Pediatric Evaluation of Disability Inventory; PK=pharmacokinetics; WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

Table 12: Schedule of Assessments (Following Recommendation by the Safety Review Committee for an Unscheduled Dose Adjustment)

Assessment	Specific Time	First Day Adjusted Dose is Administered	[redacted] Follow-Up Visit[a]
Physical examination	Any time during study visit	[redacted]	
Vital signs	Any time during study visit		
Neurologic examination	Prior to the first blood draw		
Chemistry and Hematology[b]	Any time during study visit		
Urinalysis[c]	Any time during study visit		
Seizure activity[d]	Any time during study visit		
PD sampling, urine	Any time during study visit		
PD sampling, blood	Predose		
PK sampling[e]	EOI (±5 minutes)		
PK sampling[e]	1 to 2 hours after EOI		
PK sampling[e]	3-4 hours after the EOI		
ORGN001 infusion[e]	Any time during study visit		
Assess concomitant medications/procedures	Any time during study visit		
ECG[f]	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]

[a] Patients return to the clinic [redacted] after the first day the adjusted dose is administered. Once the patient has completed the [redacted] Follow-up Visit, the patient resumes regularly scheduled study visits. 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.

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

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

[d] Changes in anticonvulsants, including the reason for the change, will be recorded.

[e] On those days where PK samples are collected, the patient's infusion of ORGN001 must be administered at the study site.

[f] Electrocardiograms should be performed prior to any blood draws or treatment administration scheduled for the same study visits.

Abbreviations: AE=adverse event; ECG=electrocardiogram; EOI=end-of-infusion; PD=pharmacodynamics; PK=pharmacokinetics.

6. SAFETY REVIEW COMMITTEE AND DATA MONITORING COMMITTEE

6.1. Safety Review Committee

To monitor patient safety, data will be reviewed regularly by the Investigator or designee throughout the study. [redacted] The SRC will review [redacted] data for each individual at the following time points:

- [redacted] in advance of the first dose adjustment [redacted]
- At any other time during the study, as requested by the Investigator or Sponsor, [redacted]

Note that the DMC also will review each patient's record [redacted], prior to any study dose escalation [redacted]. Further information on the DMC is available in Section 6.2.

[redacted] Based on SRC review of the available data, [redacted] the SRC may recommend stopping, increasing, decreasing, or maintaining (current dose) the dose of ORGN001.

The Investigator or Sponsor may also convene the SRC for unscheduled dose adjustments, based on drug-related AEs or changes in clinical parameters.

6.1.1. Safety Criteria for Unscheduled Dose Adjustments

Doses may be adjusted, based on drug-related AEs or changes in clinical parameters and laboratory data. Dose changes will occur following consultation with the medical monitor and, if applicable, with the SRC. If a patient has significant clinical worsening related to ORGN001 dosing, the dose may be decreased, based on the patient's clinical status and, if available, exposure data.

6.1.2. Criteria for Adjustment or Stopping Doses

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. Consideration of dose changes for each patient will be assessed individually by the treating physician, based on the patient's clinical status and review with the medical monitor.

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

  Action: No further dose escalations will take place in any patient; pending evaluation, all other patients will maintain their current dose level and no new patient will be enrolled in the study. A substantial amendment to the Clinical Trial Authorization will be submitted

to the relevant Competent Authorities for approval prior to restarting enrollment and allowing further dose escalations in the event that any study drug-related SAE results in the death of a single patient.

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

Action: If the treating physician, in consultation with the medical monitor, determines that a dose reduction could be expected to reduce the risk of the SAE and not increase the risk of MoCD-related symptoms, the patient may be treated with a lower dose of ORGN001. Subsequent dose escalation for that patient may be considered, based on clinical assessment by the treating physician in consultation with the medical monitor.

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

Action: In addition to the actions taken under Scenario 2, dosing in subsequent patients may be limited, to achieve concentrations below those observed in the patients with drug-related SAEs, patient to clinical assessment by the treating physician in consultation with the medical monitor.

- Scenario 4: PK exposure in a single patient exceeds the AUC NOAEL limit by greater than 10%

Action: The patient's dose is reduced to a dose level that results in exposure that is below the NOAEL exposure.

6.1.3. 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, patient care would be transferred to a different Investigator. If all centers are terminated, patients would return to the care of their treating physicians. Conditions that may warrant termination of the study or investigational sites include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- Sponsor decision to suspend or discontinue testing, evaluation, or development of the ORGN001
- Failure of the Investigator to comply with the approved protocol, pertinent guidelines, and/or regulations
- Submission of false information knowingly from the Investigator to the Sponsor and/or regulatory authorities

6.2. Data Monitoring Committee

[redacted] The DMC will have access to all safety data, in accordance with its primary function of ensuring patient safety. The DMC may make

recommendations to the Sponsor regarding safety issues, study conduct, and/or modifying, extending, or stopping the study.

[redacted]

The DMC will review each patient's record [redacted], prior to any study dose escalation [redacted]. The SRC may request additional ad hoc DMC meetings, as needed.

[redacted]

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

6.3. Definition of Study End

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

After Month 36, treatment with ORGN001 may be continued if determined to be clinically indicated. Due to the rare nature of the disease and no currently available treatment, patients exceeding 36 months of treatment may continue to receive study drug until ORGN001 becomes commercially available or development has stopped.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Recruitment and Consent

Eligible patients will be identified via prenatal diagnosis of MoCD Type A, or as soon as possible after birth, based on genetic evaluation or, if no prenatal diagnosis is made, presentation of signs and symptoms consistent with MoCD Type A. The Investigator at each site will be responsible for discussing therapeutic options for the patient with his/her parent or legal guardian.

Should a parent or legal guardian choose to enroll his/her child in this study, he/she 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 by the Investigator or his/her designee and will be allowed to read the approved Informed Consent Form (ICF). After a comprehensive description of the protocol, review of the ICF, 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 may be obtained before the Screening/Baseline Visit.

Legal guardians who have their child diagnosed with MoCD Type A prenatally may be asked to sign a separate ICF to allow study procedures to begin on their child as soon after birth as possible.

7.2. Patient Inclusion Criteria

Patients must meet all of the inclusion criteria to be considered eligible for enrollment in this study.

- Male or female neonatal patients (1 to 28 days of age [inclusive] at the time of ORGN001 administration, with day 1 of age corresponding to the day of birth), or infant (29 days to < 2 years of age) or child (2 to 5 years of age [inclusive]) with MoCD Type A, previously untreated with ORGN001 or treated with ORGN001 through the EAP
- In neonates, diagnosis of MoCD Type A, based on:
  - Prenatal genetic diagnosis, or
  - Onset of clinical and/or laboratory signs and symptoms consistent with MoCD Type A (eg, seizures, exaggerated startle response, high-pitched cry, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or SSC, elevated xanthine in urine or blood, or low or absent uric acid in the urine or blood) within the first 28 days after birth
- In infants or children, diagnosis of MoCD Type A, based on:

  - Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may be obtained after initiation of ORGN001 therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A
- Parent or legal guardian must have signed the ICF prior to any study procedures being performed

7.3. Patient Exclusion Criteria

Patients will be excluded from participating in the study if they meet any of the following criteria:

- Diagnosis other than MoCD Type A (may be determined after the initiation of study drug)
- Condition that is considered by the treating physician to be a contraindication to therapy, including evidence of abnormalities on brain imaging not attributable to MoCD, or that might otherwise interfere with the patient's participation in the study, pose any additional risk for the patient, or confound patient assessments
- Antenatal and/or postnatal brain imaging prior to initiation of treatment with ORGN001 that indicates cortical or subcortical cystic encephalomalacia, clinically significant intracranial hemorrhage, or other abnormalities on brain imaging determined by the treating physician to be clinically significant
- mGCS for Infants and Children score of less than 7 for more than 24 hours (does not apply to children less than 1 day in age)

7.4. Patient Withdrawal Criteria

The study staff should notify the Sponsor and the site monitor of all study withdrawals as soon as possible. The patient's parent/legal guardians may withdraw consent at any time. Every effort should be made to ensure that the patient's parents/legal guardians are willing to comply with study participation, prior to conducting the Screening/Baseline procedures.

Investigators may choose to discontinue a patient's treatment due to an AE, as well as conditions or illnesses that preclude compliance with the protocol from the standpoint of the patient's safety or wellbeing (safety, behavioral, or administrative reasons). Patients may be withdrawn from the study for reasons including, but not limited to:

- Diagnosis other than MoCD Type A
- The discretion of the Investigator, in consultation with the medical monitor/SRC, as appropriate, regarding an AE or other medical reason (eg, clinically significant Baseline abnormalities on MRI or brain ultrasound)
- Patient (and/or parent or legal guardian) request
- Patient and/or parent or legal guardian is unwilling or unable to adhere to the protocol requirements

All patients who discontinue or are withdrawn from the study will be encouraged to complete the Safety Follow-up Visits [redacted] following treatment discontinuation,

whenever possible. The reasons for premature study withdrawal must be recorded in the patient's CRF and in the source records.

For patients who are prematurely withdrawn from the study due to clinical findings (eg, AE[s]), the Investigator must immediately notify the Sponsor's medical monitor. In these patients, AEs leading to premature withdrawal must be followed until resolution of the event 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.

Patients who withdraw from the study will return to the care of their treating physician.

8. TREATMENT OF PATIENTS

This is an open-label study designed to evaluate the safety and efficacy of ORGN001 administered to neonates, infants, and children with MoCD Type A. All enrolled neonate patients meeting inclusion and exclusion criteria will receive treatment with study drug (ORGN001 infusion) as soon as possible after birth.

8.1. Description of Study Drug

Table 13: ORGN001 Description

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

8.2. Prior and Concomitant Medications and Procedures

Prior medications, defined as any drug or substance taken by the patient within 28 days prior to the time the parent or legal guardian signs the ICF until the first ORGN001 dose, and concomitant medications, defined as any drug or substance taken by the patient after the first ORGN001 dose until completion of the last study visit, will be recorded on the patient's CRF.

Prior procedures, defined as any therapeutic intervention (eg, surgery/biopsy, physical therapy) performed within 28 days prior to the time the parent or legal guardian signs the ICF until the first ORGN001 dose (not to exclude the collection of data on relevant procedures as part of Medical History conducted more than 28 days prior to consent), and concomitant procedures, defined as any therapeutic intervention (eg, surgery/biopsy and physical therapy) performed after the first ORGN001 dose drug until completion of the last study visit, will be recorded on the patient's CRF. If possible, elective surgical procedures should not be performed during the initial 12-month study period.

ORGN001 is not an inhibitor of cytochrome P450 (CYP450) enzymes *in vitro*; therefore, concurrent administration of ORGN001 is unlikely to affect systemic exposure of other CYP substrates. CYP isoforms responsible for biotransformation of ORGN001 are unknown.

Changes in a patient's anticonvulsants, 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.

8.3. Treatment Adherence

The Investigator or designee must ensure that the parent or legal guardian of each study patient is 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, [redacted]. If a parent or legal guardian is unable to administer ORGN001 on a given day, study drug may be administered by an alternate caregiver, provided that training for ORGN001 administration by

the alternate caregiver has been documented. Patient adherence to the study drug regimen will be monitored throughout the study by reviewing 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. Additionally, these must be documented as protocol deviations.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

ORGN001 drug product [redacted] is a sterile, nonpyrogenic, white to slightly yellow lyophilized powder in a stoppered, [redacted] vial. The drug product is designed to be reconstituted in [redacted] sterile Water for Injection and administered by IV infusion. [redacted]

9.3. Study Drug Storage

ORGN001 vials must be stored frozen at -10°C to -25°C and 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 [redacted] other than by ambient air temperature. [redacted]

9.4. Study Drug Preparation

To account for the impact of body weight on the mass (mg) of administered study drug, body weight will be assessed [redacted] The dose may be adjusted due to weight changes recorded by the home caregiver and/or physician visits with proper documentation.

Reconstitute ORGN001 with [redacted] sterile Water for Injection.

[redacted]

9.5. Study Drug Administration

Starting on Day 1, patients will begin daily IV infusions of ORGN001 at a dose of either 700 µg/kg (term neonates, infants, and children) or 525 µg/kg (preterm neonates). ORGN001 drug product is to be administered at an infusion rate of 1.5 mL/min, [redacted]. Based on a review of Day 1-related exposure parameters, each patient's dose may be initially escalated [redacted] with incremental increases up to 1200 µg/kg/day by Month 3.

[redacted] The parent, legal guardian, and any authorized caregiver will be trained on proper storage, preparation, and administration of study drug for dosing at home, [redacted].

[redacted]

9.6. 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, the date, 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.

9.7. 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, country, and/or local regulations. [redacted]

10. PHARMACODYNAMICS ASSESSMENTS

Pharmacodynamic assessments will be performed using spot urine samples collected at all study visits, and using venous blood samples collected predose .

Pharmacodynamic assessments also will be collected at Safety Follow-up Visits and any unscheduled dose adjustment visits.

An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used .

Samples will be evaluated for biomarkers of the MoCD pathway including, but not limited to: SSC,

Prior to first infusion, at least 1 blood sample and 1 urine sample must be collected.

Following recommendation by the SRC for an unscheduled dose adjustment, additional blood and urine samples will be collected to evaluate changes in SSC, xanthine, uric acid, urinary creatinine, as follows:

- On the first day the adjusted dose is administered, the patient will be administered study drug in-clinic, and a pre-dose blood sample will be collected on the day of the dose adjustment . A urine sample will be collected at any time during the dose adjustment visit.
-
- At any Safety Follow-up Visit, a PD blood sample will be collected.

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 . If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the Investigator should provide justification for the deviation.

11. PHARMACOKINETICS ASSESSMENTS

Pharmacokinetic assessments will be performed [redacted]. Pharmacokinetic samples also will be collected at Safety Follow-up Visits and any unscheduled dose adjustment visits.

An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used [redacted].

Blood samples will be collected for assessment of PK parameters (C_{max}, AUC, $t_{1/2}$). Details of PK sampling time points are specified below. Dosing date, time, amount, precise time of infusion prior to PK sample collection, and exact time of PK sample collection must be recorded in the CRF.

Pharmacokinetic samples will be collected [redacted]:

- Pre-dose at Day 1 only
- at the EOI ±5 minutes
- 1 to 2 hours after EOI
- 3 to 4 hours after EOI

If the PK collection kit is not available for Day 1 PK sample collection, samples may be drawn any time from Day 2 to Day 7, when the patient is still in the hospital. In such a case, PK samples should be collected using the following schedule:

- at the EOI ±5 minutes
- 1 to 2 hours after EOI
- 3 to 4 hours after EOI

Day 1 PK samples will be analyzed and PK assessment completed in time for a scheduled combined SRC/DMC meeting prior to each patient's recommended [redacted] dose escalation [redacted].

Following recommendation by the SRC for an unscheduled dose adjustment, blood samples will be collected for assessment of PK parameters, as follows:

- On the [redacted] 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), 1 to 2 hours after the EOI, and at 3 to 4 hours after the EOI. The time of infusion, PK

sample collection, the dose administered, and the start and stop time of IV infusion are to be recorded in the CRF. [redacted] following an unscheduled dose adjustment, a PK sample will be collected at 1 to 2 hours after EOI.

[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. EFFICACY ASSESSMENTS

Efficacy assessments are described in Sections 4.3.9, 4.3.10, 4.3.11, 4.3.12, 4.3.13, 4.3.14, 4.3.15, 4.3.16, 4.3.17, 4.3.19, 4.3.20, and 4.3.21.

13. SAFETY ASSESSMENTS

Safety assessment data are collected from the time of signing informed consent, [redacted].

[redacted]

13.1. Physical and Neurological Examination

A complete physical examination, [redacted] will be performed [redacted].

13.2. Vital Signs

[redacted] At all outpatient study visits, the vital sign measurement to be recorded in the CRF is the first set of vital signs taken.

13.3. Laboratory Assessments

[redacted] The Investigator or delegate will review, sign, and date laboratory reports, as well as indicate if abnormal results are clinically significant or not clinically significant. Abnormal results will be followed, at the discretion of the Investigator. An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used [redacted].

Following recommendation by the SRC for an unscheduled dose adjustment, blood and urine samples will be collected for assessment of hematology, serum chemistry, and urinalysis as follows:

- On the day of dose change, study drug will be administered at the study site. A urine sample will be collected.
- Seven days after the adjusted dose is administered, a blood and a urine sample will be collected at any time during this study 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]

Hematology samples will be analyzed for CBC, which includes platelet count, red blood cell (RBC) count, white blood cell count and automated differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin, hematocrit, and RBC indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration).

Serum chemistry samples will be analyzed for electrolytes, BUN, creatinine, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total serum albumin, and serum osmolality.

Urine samples will be analyzed for specific gravity, pH, glucose, protein, blood and ketones (by dipstick and microscopic examination), and urine protein to creatinine ratio.

13.4. Electroencephalogram

Standard EEGs [redacted] will be performed to monitor patients with documented or suspected seizure activity in accordance with standard of care.

13.5. Adverse and Serious Adverse Events

13.5.1. Definition of an Adverse Event

An AE is defined as any unfavorable or 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 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
- Or does not meet any of the defined conditions, but the Investigator or Sponsor considers the result as clinically significant or meeting the definition of an AE.

This definition also includes signs or symptoms resulting from misuse or abuse of the product from drug overdose, drug withdrawal, medication error, as well as outside what is foreseen in the protocol, such as drug interactions and extravasation.

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, and 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/Baseline evaluation that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, and/or convenience admissions)

13.5.2. Detection of Adverse Events

The Investigator is responsible for detecting, assessing, documenting, and reporting all AEs. All serious and nonserious AE information will be collected from the time informed consent is signed until study completion.

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 as described in Section 13.5.3.

13.5.3. Recording Adverse Events

All observed or volunteered AEs, regardless of causal relationship, must be recorded and reported.

For all AEs, the Investigator must obtain adequate information in order to:

- determine the AE outcome
- determine if the event meets criteria for an SAE
- assess the AE severity
- determine AE causality

Adverse events must be documented in clear, unambiguous medical terms. Study personnel are to be advised to refrain from using abbreviations or acronyms.

For each AE, record only the diagnosis on the AE page of the CRF. 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 AE page of the CRF with relevant diagnosis only.

All AEs that later increase in 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 on the AE page or the CRF. For medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, or transfusion), the condition/diagnosis leading to the procedure should be recorded as the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder). Withdrawal due to an AE or SAE must be clearly differentiated from withdrawal due to other reasons.

Initial AEs should be closed out, with an end date consistent with the date that the AE increased in frequency and/or severity. The new AE should be recorded on a new line of the AE page, with onset date consistent with the date of increase in frequency and or severity.

13.5.4. 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 or reaction is described as any untoward medical occurrence, that at any dose:

1. Results in death
2. Is life-threatening (NOTE: 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.)
3. Hospitalization or prolongation of hospitalization. (NOTE: Hospitalization requires inpatient or prolongation of an existing hospitalization. Adverse events that are associated with hospitalization or prolongation of hospitalization are considered SAEs). Hospitalization does not necessarily include the following:
    a. rehabilitation/hospice/nursing facility
    b. Emergency room/department visit less than 24 hours in duration
    c. Elective or preplanned admission/surgery
    d. Protocol-specified admission, or admission for a pre-existing condition not associated with either a new AE or with worsening of a pre-existing AE
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Is an important medical event

NOTE: 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 which 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 event, and both AEs and SAEs can be assessed as severe, while the term seriousness refers to an AE that has met the criteria for an SAE, as described above.

13.5.5. 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.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode if the severity of the intermittent event changes.

13.5.6. Causality Assessment

An Investigator causality assessment must be provided for all AEs. This assessment must be recorded in the CRF 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 causal association between 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 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 study drug administration exists, and the likely causal association of the event with study drug. This will be based upon the known pharmacological action of study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the clinical experience of the Investigator.
- 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, which corresponds with the known pharmaceutical profile, improves with study drug discontinuation, and/or reappears with study drug rechallenge.

13.5.7. Outcome

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

If a patient experiences an 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 one event should have an outcome of death/fatal, unless an autopsy report or Investigator states otherwise.

13.5.8. Reporting Adverse Events and Serious Adverse Events to Sponsor

All nonserious AEs must be recorded on the CRF upon awareness.

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 staff becoming aware of the events. The Investigator must complete, sign, and date the email cover page, complete the SAE CRF pages, verify accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email to the contact information provided [redacted]

[redacted]

Additional follow-up information, if required or available, should be entered into the CRF, and sent to Sponsor within 24 hours of the Investigator site or 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.

All SAEs will be recorded from the time the ICF is signed until 30 days following study completion.

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

13.5.9. Sponsor Reporting Requirements

The Sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use the current Investigator Brochure as the Reference Safety document. Serious adverse event expectedness and reporting criteria will be determined by the Sponsor from the Reference Safety document.

13.5.10. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for the study Investigators. It is the Investigator's responsibility to notify the IRB/EC of all SAEs that occur at his/her site. Investigators also will be notified of all unexpected, serious, drug-related events that occur during the study. Each site is responsible for notifying its IRB/EC of these additional SAEs.

14. STATISTICAL METHODS AND PLANNED ANALYSES

Assessments will be binned into analysis visits in such a way that the assessment closest to the target study day among all assessments observed within a window around the target day will be designated for analyses over time. The visit windows will span from above the midpoint of the target day and prior visit target day up to and including the midpoint between the target day and next visit target day.

All data collected during the study will be presented in data listings, tables, and figures as described below. Continuous variables will be summarized using mean, SD, median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency distributions. Confidence intervals will be provided for all means and percentages to aid in interpretation.

14.1. Determination of Sample Size

There will be no minimum or maximum number of patients for this study. The final sample size and determination of study success relative to efficacy will depend on the OS rate as each successive patient reaches study completion.

14.2. Analysis Populations

Safety analyses will be performed on a Safety Set, defined as all patients who received at least 1 infusion of ORGN001.

Efficacy analyses will be performed on the Full Analysis Set (FAS), defined as patients with a confirmed diagnosis of MoCD Type A who have no antenatal and/or postnatal brain imaging prior to initiation of treatment with ORGN001 that indicates cortical or subcortical cystic encephalomalacia or clinically significant intracranial hemorrhage.

Additionally, two modified Full Analysis Sets (mFAS) will be used to support the analyses on the FAS:

- Neonate mFAS (NmFAS), [redacted]
- Pediatric mFAS (PmFAS) [redacted]

Available efficacy data of all patients excluded from the FAS will be displayed in listings and described in narratives.

14.3. Efficacy and Pharmacokinetic Endpoints

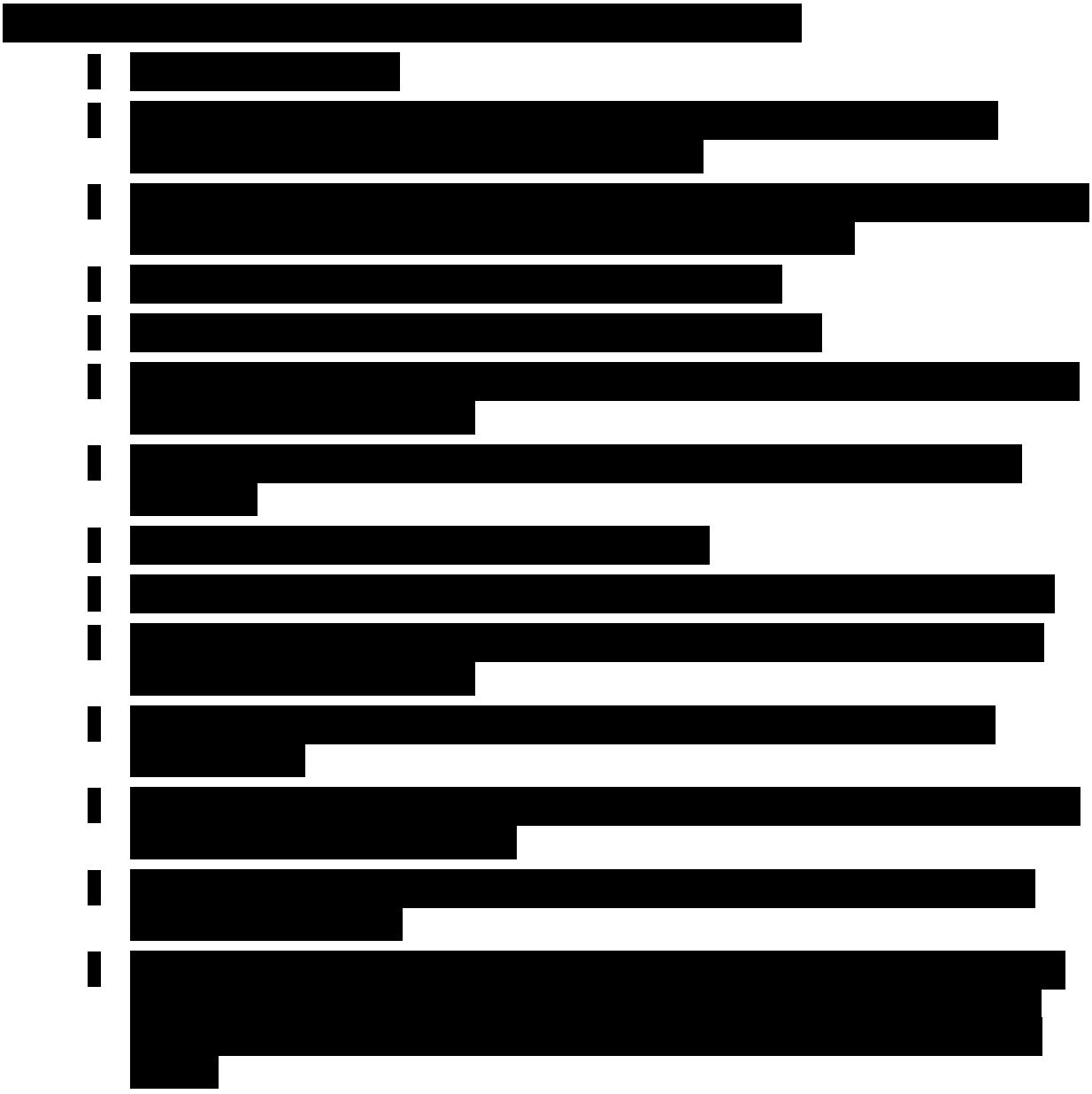
Primary Efficacy Endpoint:

- The primary efficacy analysis will be OS

Secondary Efficacy Endpoints:

[redacted]

- Changes in growth parameters (height, weight, BMI, head circumference) through Month 12
- Feeding pattern assessments through Month 12
- GMFCS-E&R results through Month 12
- Bayley-III Cognitive and Motor scaled scores and composite scores, as well as percentile ranks and age equivalents, through Month 12 (or WPPSI-IV scores, if applicable)
- The normative standard and scaled scores from the PEDI Functional Skills scales, including Self-Care, Mobility, and Social items through Month 12
- GMFM-88 results through Month 12



14.4. Demographics and Baseline Characteristics

All demographic and Baseline characteristics information will be summarized for the Safety Set, the FAS, the NmFAS, and the PmFAS.

14.5. Patient Disposition and Extent of Exposure

The number of patients screened, treated, continuing treatment after confirmation of enrollment criteria, and completing the 12-month and 36-month study periods will be tabulated. Reasons for any patient withdrawals will be provided. The number of patients in the safety and efficacy analysis sets, along with reasons for exclusion from analysis sets, will be tabulated.

Extent of exposure with ORGN001 will be summarized among both the Safety Set and FAS, with respect to number of infusions, number of missed and partial infusions, and duration of treatment period.

14.6. 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 anticonvulsants.

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

14.7. Efficacy Analyses

Efficacy analyses will be performed on the FAS, NmFAS, and PmFAS. Baseline is defined as the last available assessment prior to treatment with ORGN001.

14.7.1. Use of Natural History Study ALX-MCD-502

Data from natural history study ALX-MCD-502 will be used to support the current study in order to guide interpretation by representing the expected clinical time course for patients with MoCD Type A in the absence of ORGN001 treatment.

14.7.2. Primary Efficacy Analysis

The primary efficacy analysis will summarize OS, defined as the interval in months from the date of birth to the date of death or date last known alive (patients still on study will be censored at the data cutoff date), whichever occurs first.

The analysis of OS will be based on the Kaplan-Meier methodology for estimation of survival parameters. The median duration of OS will be estimated based on the 50th percentile of the Kaplan-Meier distribution; additional summary statistics, including the 25th and 75th percentiles, 95% confidence intervals (CIs) on the median and the other percentiles and proportion of censored patients. The analysis of OS will be done using the FAS, the NmFAS, and the PmFAS.

14.7.3. Secondary Efficacy Analyses

[redacted]

Body weight, length, head circumference, and BMI will be analyzed by converting each parameter to age-adjusted z-scores and age percentiles, and descriptive statistics will be presented to each parameter through Month 12.

Changes in motor function through Month 12 will be summarized based on data from the administration of the GMFCS-E&R, which is a 5-level classification system that classifies gross motor functional capabilities and limitations as usual performance in the home, school, and community setting.

The Bayley-III Cognitive and Motor scaled scores and composite scores, as well as percentile ranks, and age equivalents will be summarized through Month 12. Where appropriate, the WPPSI-IV will be used instead of the Bayley-III.

Changes in PEDI standard and scaled scores will be summarized by self-care, mobility, and social function domains through Month 12.

Changes in gross motor development will be summarized through Month 12 based on data from the administration of the GMFM-88, which measures patient-initiated motor activities in 5 dimensions: Lying and Rolling; Sitting; Crawling and Kneeling; Standing; and Walking, Running, and Jumping. A percent score can be obtained for each dimension and for the total of all GMFM dimensions. Patients who use mobility aids and/or orthoses will be assessed without those aids.

All secondary efficacy analyses will be done using the FAS, the NmFAS, and the PmFAS.

[redacted]

[redacted]

14.8. Safety Analyses

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

14.8.1. Adverse Events

All AEs arising after signing the ICF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 22.0 or higher) and displayed in listings.

[redacted]

[redacted]

Treatment-emergent adverse events are AEs with onset on or after the first date of ORGN001 administration. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and Preferred term for all events and those considered at least possibly related (including missing relationship) to ORGN001 by the Investigator, both overall and by severity. Serious TEAEs will be tabulated by SOC and Preferred term.

Summaries will include both the number of patients affected and the number of events. For patient counts in summaries by severity or relationship, 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 in the most extreme category of severity or relationship observed.

14.8.2. Laboratory Parameters

Incidence of abnormalities for clinical laboratory assessments (chemistry and hematology) will be summarized by visit. Laboratory analytes and their changes from baseline will be summarized by visit.

14.8.3. Physical Examinations and Vital Signs

Adverse physical examination changes will be reported as AEs and analyzed as such. Vital signs and their changes from baseline will be summarized by visit.

14.8.4. Electrocardiograms

Listings of ECG results will be produced.

14.8.5. Electroencephalograms

Listings of EEG results will be produced.

14.9. Pharmacokinetic Analysis

Plasma concentration-versus-time profiles will be graphically summarized. Plasma concentration and PK parameter summaries will include descriptive statistics, as appropriate. [redacted]

14.10. Other Statistical Issues

14.10.1. Computing Environment

Efficacy and safety analyses will be performed using SAS for windows, Version 9.3 or higher (SAS Institute Inc., Cary, NC, USA).

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

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

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

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

During the study, a Sponsor's representative 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, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of data in the CRFs 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 that AEs and SAEs have been properly documented on CRFs, and confirm that any SAEs have been forwarded to the Sponsor. Confirm that SAEs meeting 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.

15.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an EC, 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 examine systematically and independently all study-related activities and documents, to determine whether study-related activities were conducted, and whether data were recorded, analyzed, and accurately reported, according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board/Ethics Committee

The Investigator must obtain IRB/EC approval for the investigation. All IRB/EC approvals, including initial and continued review, and all materials approved by the IRB/EC for this study, including the ICF and any recruitment materials must be maintained by the Investigator and made available for inspection.

16. 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 15.2).

17. 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 with 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 from procedures (eg, topical anesthesia to place IV catheters, use of indwelling catheters rather than repeated venipunctures for blood sampling, and collection of some protocol-specified blood samples when routine clinical samples are obtained).

17.1. 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 EC, as appropriate. The Investigator must submit written approval to the Sponsor before he/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 scientific validity of the study will require IRB/EC 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 Investigator is responsible for informing the IRB or EC of any amendment to the protocol, in accordance with local requirements. In addition, the IRB or EC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB or EC upon receipt of amendments and annually, as local regulations require.

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

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

17.2. Written Informed Consent

The Investigator 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 possible benefit of the study. The patient's parent or legal guardian also must be notified that he/she is free to discontinue his/her child from the study at any time. The parent or legal guardian should be given the opportunity to ask questions and time to consider the information provided.

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

The Investigators 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 study that might affect parent or legal guardian willingness to continue study participation, the parent or legal guardian will be notified in a timely manner about the new information and asked to sign a new ICF.

17.3. Patient Data Protection

Prior to performing 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.

Case Report Forms will be completed at the site either on paper or in the electronic data capture (EDC) system. Copies of pertinent records in connection with the study, eg, patient charts or laboratory data, will be made available to the Sponsor or designee on request, in a timely manner throughout the study, with due precaution toward protecting patient privacy.

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

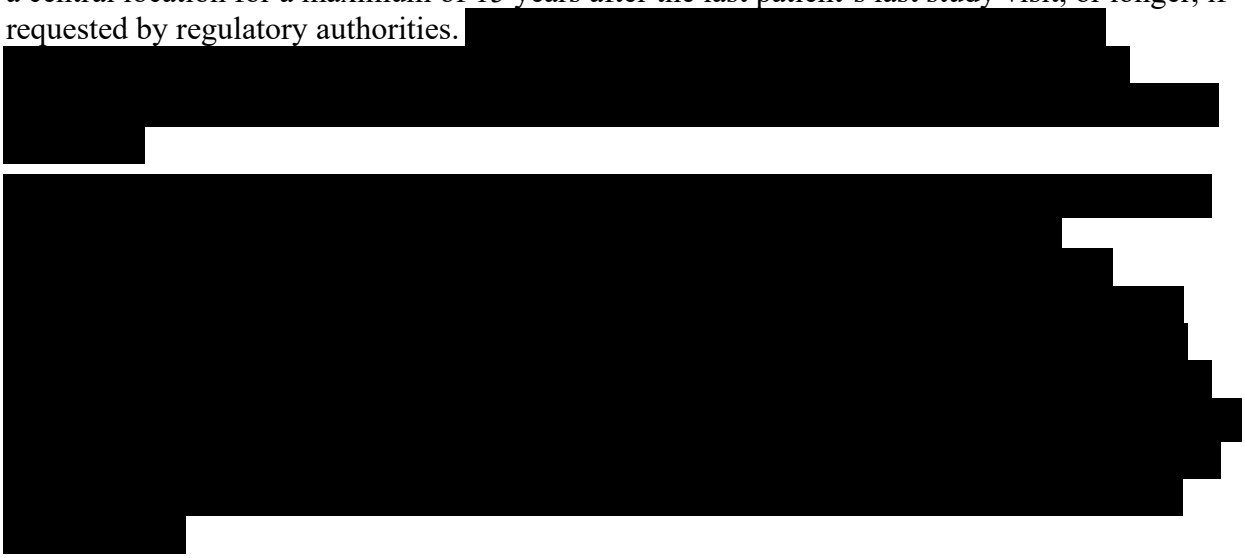
The Sponsor or designee will be allowed to conduct site visits for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts, study source documents, and other records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

18.2. Retention of Records

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

18.3. Retention of Biological Samples

If a patient's parent or legal guardian has provided consent for long-term storage of biological samples, and if permitted by local regulatory authorities, any remaining samples 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.



Study samples and data for biochemical analysis will be single-coded. The link between a patient enrollment number and any biochemical results will be maintained and stored in a secure environment with restricted access. The link will be used to identify relevant samples for analysis, facilitate correlation of biochemical results with clinical data, allow regulatory audit, and trace samples for destruction in the case of consent withdrawal, 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 results of this research.

18.4. 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. 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.

19. 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.

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APPENDIX A. BLOOD SAMPLING VOLUMES

[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.
2. 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.
3. EMLA (eutectic mixture of local anesthetics) cream/plaster: To minimize the possible pain and discomfort due to collection of blood, the Investigator should apply an EMLA cream/plaster at the puncture site.

References:

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APPENDIX B. BLOOD SAMPLING VOLUMES TABLES

Table 15: Blood Sampling Volumes (in mL) During the 12-Month Study Period

Sample	Marker or Specific Time	Screening/ Baseline Day[a] -1	[redacted]
Genotype (if not previously done)		[redacted]	
Serum Chemistry[b]			
Hematology[b]			
Biochemical PD Markers	SSC, [redacted]		
ORGN001 PK[c]	Pre-dose		
	EOI		
	1-2 hours after the EOI		
	3-4 hours after the EOI		
[redacted]			
Total amount per time point (mL)			

[a] Screening/Baseline and Day 1 sampling can be performed on the same day.
[b] Chemistry and hematology samples will be assessed [redacted]. Capillary samples may be considered if collecting venous samples is not possible.
[c] Pharmacokinetic sampling will be performed on the first day of any dose increase.

[redacted]

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

Table 16: Blood Sampling Volumes During the Long-Term Extension Period, After a Dose Adjustment, and at the Safety Follow-up

Sample	Marker or Specific Time	Long-Term Extension Period	Visits after an Unscheduled Dose Adjustment	Safety Follow Up [redacted]
[redacted]				
Serum Chemistry [a]				
Hematology [a]				
Biochemical PD Markers	SSC, [redacted]			
ORGN001 PK [b]	EOI			
	1-2 hours after the EOI			
	3-4 hours after the EOI			
[redacted]				

[a] Chemistry and hematology samples will be assessed [redacted]. Capillary samples may be considered if collecting venous samples is not possible.
[b] Pharmacokinetic sampling will be performed on the first day of any dose adjustment.
Abbreviations: EOI=end of infusion; mL=milliliters; PD=pharmacodynamic; PK=pharmacokinetics; SSC=S-sulfocysteine; [redacted]

APPENDIX C. MODIFIED GLASGOW COMA SCALE FOR INFANTS AND CHILDREN

Modified Glasgow Coma Scale for Infants and Children

Area Assessed	Infants	Children	Score[a]
Eye opening	Open spontaneously	Open spontaneously	4
	Open in response to verbal stimuli	Open in response to verbal stimuli	3
	Open in response to pain only	Open in response to pain only	2
	No response	No response	1
Verbal response	Coos and babbles	Oriented, appropriate	5
	Irritable cries	Confused	4
	Cries in response to pain	Inappropriate words	3
	Moans in response to pain	Incomprehensible words or nonspecific sounds	2
	No response	No response	1
Motor response[b]	Moves spontaneously and purposefully	Obeys commands	6
	Withdraws to touch	Localizes painful stimulus	5
	Withdraws in response to pain	Withdraws in response to pain	4
	Responds to pain with decorticate posturing (abnormal flexion)	Responds to pain with decorticate posturing (abnormal flexion)	3
	Responds to pain with decerebrate posturing (abnormal extension)	Responds to pain with decorticate posturing (abnormal extension)	2
	No response	No response	1

[a] Score:
≤ 12 suggests a severe head injury
≤ 8 suggests need for intubation and ventilation
≤ 6 suggests need for intracranial pressure monitoring

[b] If the patient is intubated, unconscious, or preverbal, the most important part of the scale is motor response. This section should be carefully evaluated.

Adapted from Davis RJ et al: Head and spinal cord injury. In Textbook of Pediatric Intensive Care, edited by MC Rogers. Baltimore, Williams & Wilkins. 1987; James H, Anas N Perkin RM: Brain Insults in Infants and Children. New York,. Grune & Stratton, 1985; and Morray JP et al: Coma scale for use in brain-injured children. Critical Care Medicine. 12:1018. 1984.

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