A Phase 2A Open-Label Study Evaluating the Safety and Efficacy of Low-Dose Ketamine in Children with ADNP Syndrome
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A Phase 2A Open-Label Study Evaluating the Safety and Efficacy of Low-Dose Ketamine in Children with ADNP Syndrome

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[DATE OF MEETING]

[TIME], EST

The goal of the proposed research is to conduct a Phase 2A, single dose, open-label study to evaluate the safety and tolerability of low-dose ketamine in children with ADNP syndrome. Ketamine is commercially available and FDA approved as an anesthetic for children in the proposed age range. At the conclusion of this study, we expect to demonstrate the safety and tolerability of low-dose ketamine in children with ADNP syndrome and anticipate identifying meaningful signals of efficacy in clinical outcome measures to inform future phase 3 studies.

Research design. The proposed study utilizes a single-dose (0.5 mg/kg), open-label design to investigate the safety, tolerability, and efficacy of treatment with low-dose ketamine in children with ADNP syndrome, ages 5 to 12. The study will comprise a: (1) Screening period which will take place within the 4 weeks preceding a Baseline visit; (2) Baseline visit on day 0 for baseline assessments and administration of study drug; (3) Clinic visits for safety and efficacy assessments at weeks Day 1, week 1, 2, and 4.

Inclusion criteria: The proposed study will recruit 10 children between 5 and 12 years-old with ADNP syndrome, many of whom will have already been previously evaluated as part of ongoing studies at the Seaver Center. All subjects will have a Clinical Global Impression-Severity score of 4 (moderately ill) or greater at screening (see Outcome Measures section). Subjects will also be on stable medication, including anti-epileptic and/or behavioral medications, supplements, and special diets, must be at a stable dose for at least 4 weeks prior to enrollment. Participants must also meet age-specific blood pressure criteria based on recommended guidelines.

Exclusion criteria: Cases will be excluded if any of the following are applicable: 1) Has a concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease) or condition or any clinically significant finding at screening that could interfere with the conduct of the study or that would pose an unacceptable risk to the subject in this study, 2) Has clinically significant lab abnormalities or vital signs at the time of screening (e.g., alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal; total bilirubin or creatinine >1.5 × upper limit of normal). Re-testing of safety labs is allowed, 3) Hypertension that is not well controlled (systolic BP >130-140 mm Hg or diastolic BP >85-95 mm Hg depending on age), 4) have caretakers who are unable to speak English, be consistently present at visits to report on symptoms, or are otherwise judged unable to comply with the protocol by the study team; 5) A blood pressure reading over 160/90 or two separate readings over 140/90 at screening or baseline visits, 6) Thyroid impairment, as reflected by a TSH > 4.2 mU/L, 7) Cardiac disease, as reflected by an EKG that is abnormal and of concern for cardiac disease, 8) Has had changes in his/her medication regimen within the previous month, 9) Has a history of uncontrollable seizure disorder or seizure episodes within 1 month of screening, 10) Has a history of suicidal behavior or considered by the investigator to be at high risk of suicide, 11) Has a current or past history of psychotic symptoms, 11) Has enrolled in any clinical trial or used of any investigational agent, device, and/or investigational procedure within the 30 days before screening or does so concurrently with this study.

Drug Administration: The proposed dose is a single daytime infusion. Dosing is based on data derived from previous pre-clinical and clinical studies in children and adults and will follow a pre-fixed dosing paradigm according to patients' weight. Intravenous dosage will be 0.5 mg/kg over 40 minutes. The pharmacist will prepare the IV medication (ketamine) in a normal saline (NS) bag, and a nurse from the General Clinical Research Center (GCRC) at Mount Sinai or the Clinical Research Coordinator comes to retrieve it the morning of infusion, such that a fixed dose is administered. Each participant will receive an infusion of 0.5 mg/kg of racemic ketamine hydrochloride, which is dissolved in 0.9% saline in a total volume of 50 mL and administered with an infusion pump (Baxter, Deerfield, Ill) at a constant rate over 40 minutes. The ketamine will be stored and dispensed by Ivy Cohen and the research pharmacy at Mount Sinai.

Active monitoring throughout the infusion and for one hour thereafter will ensure safety and tolerability. Tolerability will then be assessed by the research physician throughout the study. Vital signs and EKG will be monitored continuously during the infusion with a non-invasive blood pressure reading taken every 5 minutes and with continuous EKG and pulse oximetry. Following the infusion, the patient will have continuous EKG and pulse oximetry with blood pressure cycled every 15 minutes for at least one hour once it is within 20% of baseline. The patient will continue to be monitored clinically for one hour post-infusion. In addition to the pediatric anesthesiologist, clinical monitoring will also be done by the principal investigator (PI) who is a board certified child and adolescent psychiatrist with expertise in ADNP syndrome. The PI will be present throughout the entire infusion and for one hour thereafter in order to closely monitor and assess emergency phenomena (e.g., agitation, hallucinations, dissociation, bizarre behavior). Because individuals with ADNP syndrome are intellectually disabled and mainly nonverbal, close clinical observation is the best method to monitor these types of emergency phenomena. Should any agitation or bizarre behavior occur during the infusion, the infusion will be discontinued. Should these phenomena occur after the infusion, they will be recorded on the side effects log (i.e., SLAES). To meet criteria for discharge, patients will be fully awake and alert with mental status returning to pre-infusion baseline and have at least two consecutive vital signs that are within 20% of baseline.

Adverse Events (AEs): All subjects will be evaluated for study drug safety and tolerability using physical examination, laboratory assessments, and the Systematic Longitudinal Adverse Events Scale (SLAES). All patients will have a physical examination and specific laboratory tests as including: physical exam, electrocardiogram (ECG), vital signs, complete blood cell counts, electrolytes, thyroid functioning test, liver function tests, and urinalysis. A urine pregnancy test will be performed in post-pubertal girls. Results of these tests will identify patients who should be excluded because of active medical problems that might make study participation unsafe.

An AE will be defined as any untoward medical occurrence in a study subject, temporally associated with the use of the experimental medication, whether or not considered related to the medication. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study drug. A serious adverse event (SAE) will be defined as an AE that meets any of the following criteria:

- is life threatening;
- requires inpatient hospitalization;
- results in a persistent or significant disability/incapacity;
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above

Monitoring for AEs will be conducted during scheduled and unscheduled visits, if clinical concerns arise. Safety and tolerability aspects of the data will be tabulated. Assessments will include the frequency and severity of treatment-emergent adverse events (TEAEs) and SAEs, medication diary, concomitant psychosocial and medication treatment log, clinical evaluations including a physical exam and vital sign measurements, height and weight. All safety and laboratory assessments will be completed at Screening and all Clinic Visits.

The goals of this DSMB meeting are to review the research protocol and safety data to date. The session will include review of administrative reports that describe participants screened, enrolled, and completed, as well as baseline characteristics of the study population. All of the 10 screened participants have been enrolled and administered the study drug; no participants have withdrawn from the study to date. The study is closed to enrollment as recruitment goals were met. All study visits and data collection has been completed. The study remains open for data analysis.