CLINICAL PROTOCOL

NCT02852213

A SINGLE-STAGE, ADAPTIVE, OPEN-LABEL, DOSE ESCALATION SAFETY STUDY OF ADENO-ASSOCIATED VIRUS ENCODING HUMAN AROMATIC L-AMINO ACID DECARBOXYLASE (AAV2-hAADC) ADMINISTERED BY MR-GUIDED CONVECTIVE INFUSION INTO THE MIDBRAIN IN PEDIATRIC PATIENTS WITH AADC DEFICIENCY

IND Number: 16127

Initial Clinical Site:

University of California San Francisco

1 PROTOCOL SYNOPSIS

STUDY TITLE

A Single-Stage, Adaptive, Open-Label Dose Escalation Safety Study of Adeno-Associated Virus Encoding Human Aromatic L-Amino Acid Decarboxylase (AAV2-hAADC) Administered by MR-guided Infusion into the Midbrain in Pediatric Patients with AADC Deficiency

INVESTIGATIONAL PRODUCT

The AAV2-hAADC vector consists of an adeno-associated virus, serotype 2 (AAV2) containing human AADC complementary DNA (cDNA), human cytomegalovirus (CMV) promoter and 3'UTR sequences. Study drug is provided in a sterile formulation of phosphate buffered saline with 0.001% Pluronic acid (F-68). AAV2-hAADC is supplied in 0.5 mL aliquots as a suspension at a target concentration of 4.9×10^{12} vector genomes per mL.

The vector and excipient for dilution will be supplied to the clinical site by the Clinical Vector Core, Children's Hospital of Philadelphia.

The parenchymal use of gadoteridol is off-label, and also part of this study.

CLINICAL PHASE

Phase 1. Given the extremely rare nature of the disease and limited number of subjects, this study will generate data for dose selection, evaluation of safety, and confirmatory evidence of efficacy. A single stage study will address dose selection and a future study will further evaluate safety and efficacy of the selected dose.

STUDY OBJECTIVES

The overall objective of this study is to determine the safety and efficacy of AAV2-hAADC delivered to the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) in children with aromatic L-amino acid decarboxylase (AADC) deficiency. Specifically, the study will assess:

- Safety, as measured by adverse events (AEs), safety laboratory tests, brain imaging, and the relationship of AEs to study/surgical procedures or to AAV2-hAADC.
- Clinical responses to treatment with AAV2-hAADC. The primary clinical outcomes will reflect the predominant motor deficits of loss of motor function and dystonic movements.

STUDY RATIONALE

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare recessive genetic disorder in which mutations in the gene encoding the AADC enzyme lead to deficient synthesis of catecholamines (dopamine, norepinephrine, epinephrine) and serotonin. Over 100 cases have been identified worldwide since the original description of the disorder in 1990. Affected children suffer chronic and severe motor, cognitive, and behavioral disability. The most prominent neurological symptoms are motor: hypokinesia, hypotonia, oculogyric crises, involuntary

movements and motor developmental delay. Additional symptoms include emotional lability, sleep disturbance, and hypotension. Because of the specific location of the metabolic block in this disorder (the conversion of levodopa to dopamine), motor symptoms do not respond to therapy with levodopa, in contrast to the positive response observed in Parkinson's disease and in other inborn errors of dopamine metabolism. Most patients with AADC deficiency derive little or no benefit from currently available medical therapies.

In recent years, use of a viral vector, adeno-associated virus type 2 (AAV2), encoding the human AADC gene (hAADC), has been developed for the treatment of Parkinson's disease. Early studies have demonstrated that the gene can be safely delivered to the striatum in human subjects via targeted infusion. The current protocol proposes to adopt a similar strategy to deliver AAV2-AADC to select midbrain regions to treat AADC deficiency in pediatric patients.

STUDY POPULATION

Male and female patients aged 5-18 years with a confirmed diagnosis of AADC deficiency who, in the Investigator's opinion, are candidates for surgical therapy and who meet all inclusion/exclusion criteria, will be enrolled.

The initial patients screened for this study will be those with severe motor impairment and motor developmental delay despite treatment with currently available medications. The selection of patients who have failed to benefit from existing treatments will exclude newly diagnosed patients, as it would take at least 12 months to evaluate response to medications and determine lack of motor benefit.

For the first group of 3 subjects (Group 1), the primary goal is to assess procedural safety. The minimum age for the first group of patients will be 5 years. The selection of this lower age limit is intended to minimize the risks because response to standard therapy is less certain in younger children, and there are increased risks associated with skull fixation in very young children. Based on previous clinical experience in the treatment of neurotransmitter disorders, younger patients may have the potential to benefit the most from AADC gene transfer. Thus, the Investigator will contact the Agency after the first few subjects have been treated to discuss modifying the age requirement to enroll younger patients. Although it is anticipated that younger patients may have greater potential than older patients to benefit from AADC gene transfer, there is no specific evidence that older patients would not also benefit.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

1. Definite diagnosis of AADC deficiency, confirmed by at least two of the following three criteria: (1) CSF neurotransmitter profile demonstrating reduced HVA and 5-HIAA, and elevated 3-OMD concentrations, (2) plasma AADC activity less than or equal to 5 pmol/min/mL, (3) molecular genetic confirmation of homozygous or compound heterozygous mutations in DDC.
2. Age 5 years to 18 years (note: we will contact the Agency after the first few subjects have been treated to discuss modifying the age requirement to enroll younger patients).

3. Failed to derive adequate benefit from standard medical therapy (dopamine agonists, monoamine oxidase inhibitor, pyridoxine or related form of Vitamin B6).
4. Unable to ambulate independently (with or without assistive device)
5. Cranium sufficiently developed, with sutures closed, to enable surgical placement of SmartFrame® system on the skull for MRI-guided stereotactic targeting.
6. FDOPA PET and DAT SPECT imaging findings consistent with the diagnosis of AADC deficiency.
7. Brain MRI does not show any conditions or malformations that are clinically significant with respect to risks for stereotactic brain surgery.
8. Parent(s)/guardian(s) of the study subject must agree to comply with the requirements of the study, including the need for frequent and prolonged follow-up.
9. Both parents (or legal guardians) must give their consent for their child's participation in the study.
10. Stable medication regimen for treatment of AADC deficiency: no new medications introduced for at least 6 months, and no existing medication dose changes for at least 3 months prior to Baseline.
11. Baseline hematology, chemistry, and coagulation values within the normal pediatric laboratory value ranges, unless in the Investigator's judgment, the out of range values are not clinically significant with respect to subject suitability for surgery.

Exclusion Criteria

1. Intracranial neoplasm or any significant structural brain abnormality or lesion (e.g., severe brain atrophy, white matter degenerative changes), which, in the opinion of the clinical investigators, would confer excessive risk and/or inadequate potential for benefit.
2. Presence of other significant medical or neurological conditions that would create an unacceptable operative or anesthetic risk (including congenital heart disease, respiratory disease with daytime home oxygen requirement, prior history of serious anesthesia complications during elective procedures, history of cardiorespiratory arrest), liver or renal failure, malignancy, or HIV positive.
3. Significant musculoskeletal abnormalities resulting from chronic, severe neurological impairment (scoliosis >45 degrees, severe joint deformity, joint contractures).
4. Previous stereotactic neurosurgery.
5. Coagulopathy, or need for ongoing anticoagulant therapy.
6. Contraindication to sedation during surgery or imaging studies (FDOPA PET, DAT SPECT, or MRI scans).
7. Neutralizing antibody titer to AAV2 ≥ 1:1200.

8. Receipt of any investigational agent within 60 days prior to the Baseline and during study participation.
9. Evidence of clinically active infection with adenovirus or herpes virus on physical examination.

PRIMARY ENDPOINTS

Safety: Assessment of AE or SAE and its relationship to study surgery, infusion, or treatment effect (graded as definite, probable, possible, unlikely or unrelated).

- Adverse Events and Serious Adverse Events
- Post-operative MRI and/or CT (with contrast if clinically indicated)
- Clinical laboratory assessments (hematology, chemistry, immunology)

Biological Activity: Demonstration of effective restoration of AADC function by assays of CSF neurotransmitter metabolites and F-DOPA PET imaging.

SECONDARY & EXPLORATORY ENDPOINTS

To obtain preliminary data regarding the potential for clinical responses by assessing the magnitude and variability of changes in clinical outcome parameters.

The principal clinical outcome measures are:

- Motor function, as assessed by the Gross Motor Function Measure (GMFM-88)
- Frequency of oculogyric episodes, as measured by a Symptom Diary

Secondary clinical outcome measures include:

- Assessment of subject disability, as assessed using the Pediatric Evaluation of Disability Inventory (PEDI); adaptive behavior, as assessed using Vineland Adaptive Behavior Scale; Patient's Global Impression of Change (PGI-C); and quality of life, as determined using the Pediatric Quality of Life Inventory (PedsQL).

It is anticipated that the utility of established developmental and cognitive assessments may be limited because of the study population's severe physical disability. Such developmental assessments include:

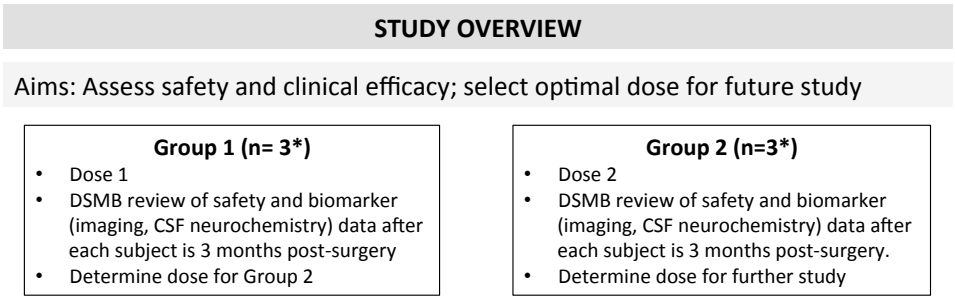
- Peabody Developmental Motor Scales 2nd edition (PDMS-2)
- Bayley Scales of Infant Development, 3rd edition.

STUDY DESIGN

This study is an adaptive, single-stage dose-escalation, open-label safety study of AAV2-hAADC delivered by real-time image-guided convection-enhanced delivery bilaterally into the substantia nigra pars compacta and the ventral tegmental area of pediatric patients with AADC deficiency.

There will be 6 subjects divided into two groups of 3. The primary aim of this study is to determine the dose for future studies based on safety, biomarkers of pharmacological activity of AADC and clinical outcomes.

Subjects will be enrolled sequentially into 2 dose groups, Group 1 followed by Group 2.



Group 1 will consist of three (3) subjects that meet the inclusion criteria will receive a single low dose of AAV2 hAADC (1.3×10^{11} vector genomes (vg), delivered as an infusate volume of up to 160 µL of vector at concentration of 8.3×10^{11} vg/mL). The total AAV2-hAADC dose will be infused bilaterally via magnetic resonance (MR)-guided convective infusion into a total of up to 4 sites per subject in both the SNc and VTA (left and right). The infusate will be divided between the VTA and SNc (e.g., 30 μL into the VTA and 50 μL into the SNc). The inter-subject dosing interval will be no shorter than 90 days for the first 3 subjects.

A Data and Safety Monitoring Board (DSMB) will be established to review safety data after each subject has been treated and will review the accumulated safety and efficacy data of Group 1. The DSMB report will be submitted to the FDA for review before Group 2 may commence. The DSMB will be notified of dose limiting toxicities (DLT) (see ***Dose-limiting Toxicity*** for definition) within 5 business days of the initial report to the PI. If none of the first 3 subjects in Group 1 experiences a DLT that results in hospitalization beyond 90 days post-surgery, enrollment in Group 2 may commence. If 1 subject experiences a DLT, treatment of additional subjects will not proceed until review and approval of the DSMB. If 2 or more subjects experience a DLT, both treatment and enrollment will be stopped, pending DSMB review. The occurrence of serious safety problems may lead to discontinuation of further treatments, based on pre-determined Stopping Rules.

The vector dose (volume and/or concentration) may be adjusted after the treatment of <3 subjects in Group 1 if the study team, DSMB, and study Advisory Committee determine, based on review of available data, that dose escalation or reduction is warranted. If dose escalation is warranted, total vg in Group 2 will be increased by factor of 3.1 (Table 2). Volume of infusion will remain constant between Group 1 and Group 2.

The final analysis of the safety and clinical outcome assessments will be performed 1 year post-surgery. A follow-up analysis will be performed 2 years post-surgery. Thereafter, subjects will be enrolled in a long-term follow-up study to assess safety and clinical status updates.

RECRUITMENT

Subject recruitment will be conducted via 3 main sources: (1) collaboration with two foundations, the Pediatric Neurotransmitter Diseases (PND) Association (USA), and the AADC Research Trust (UK), which both maintain registries of children with AADC deficiency; (2) the International Working Group on Neurotransmitter Related Disorders (iNTD), a group of physicians who treat patients with AADC deficiency, and (3) notification about the trial through the following organizations and societies: the National Organization for Rare Diseases (NORD), Genetic Alliance, Child Neurology Society mailing list, ChildNeuro Listserve. Study information will be available on Clinicaltrials.gov and a study website.

SUBJECT NUMBER

A total of up to six (6) subjects are planned to be enrolled and treated in this study

TREATMENT DURATION

Eligible subjects who have parental consent to be part of the clinical study must have screening evaluations and baseline functional testing over a period of up to three months prior to surgery. Subjects who at the time of surgery still meet all Eligibility Criteria will undergo surgery to deliver the gene vector in a single surgery. Given the nature of gene transfer, the duration of the treatment is expected to be life-long, hence we anticipate the need for a separate long term follow-up study.

DURATION OF FOLLOW-UP

Systematic clinical assessments will occur over a 24-month period postoperatively. Patients will be monitored for at least 5 years in a Long Term Follow-up Study to the protocol. Permission for autopsy studies will be requested for all patients who die during the study.

DOSE LEVEL (S) AND DOSE JUSTIFICATION

The dose levels chosen for this study are based on results obtained from analysis of a safety study in non-human primates, in which the clinical cannula and surgical procedure were used, as well as GMP-process-comparable AAV2-hAADC vector. Relevant volumes of anatomical target structures were used to provide planned dose levels in this study.

DATA ANALYSIS PLAN

All subjects who received study medication will be included in the analysis of the safety and efficacy data.

Safety data will be summarized for the total study population and will be further broken down by the dose level. Treatment-emergent adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by body system and preferred term. In addition, separate summaries will be provided for treatment-emergent adverse events by severity and relationship to study drug, as well as adverse events leading to study drug discontinuation

and serious adverse events. The tolerability will be assessed by number of patients having DLTs and with premature discontinuations of study treatment.

For the evaluation of efficacy, there will be two primary clinical outcome measures:

- Motor Function, as assessed by the Gross Motor Function Measure (GMFM-88). The GMFM-88 total score will be used as the endpoint. The total score will be derived as an unweighted average of the 5 dimension scores: lying and rolling (17 items); sitting (20 items); crawling and kneeling (14 items); standing (13 items) and walking, running, and jumping (24 items). Each dimension score will be defined as % of maximum score for the dimension in question.
- Frequency of oculogyric episodes, as measured by a Symptom Diary: each recorded episode will be classified as mild, moderate or severe. The area under the curve (AUC) of the diary symptoms will be used as the endpoint. The AUC will be calculated for each study month as a sum of duration of symptoms (hours) multiplied by the severity (0-3) of the symptom in question. The endpoint is the change from baseline (average of 3 months preceding the baseline) to 1 year (average of 3 months preceding the visit at Month 12.

All data collected during the study will be used for the evaluation of the primary clinical outcome measures. The evaluation will be focused on the following comparisons:

- Change from baseline to one year in all patients treated with the selected dose level (primary comparison). However, if no dose-response is seen at Stage 1 of the study, both dose levels will be included in the primary comparison.
- Difference in change from baseline to one year between the patients treated with the selected dose level and the other dose level used.

In addition to the comparisons defined above, efforts will be made to compare the changes seen in the present study to natural progression of the disease as assessed in external natural history studies. These comparisons may involve comparison of the changes between the treated patients from the present study and untreated patients from the natural history study, using endpoints derived from the elements of the primary outcome measures. The definition of these endpoints depends on the availability of the natural history data.

MEDICAL MONITOR AND DATA SAFETY MONITORING BOARD

A Medical Monitor with clinical expertise in pediatric movement disorders will be responsible for the review of all safety and adverse experience data.

A Data Safety Monitoring Board, consisting of a minimum of 3 individuals with broad expertise in pediatrics, neurology, and gene transfer will be appointed.

DOSE LIMITING TOXICITY

Dose-limiting toxicity will be defined as any Grade 3 or 4 toxicity (NCI CTCAE v.4) that is thought to be possibly or probably related to AAV2-hAADC.

If none of the first 3 subjects experiences a Dose Limiting Toxicity (DLT) that results in hospitalization beyond 90 days post-surgery, more subjects may be enrolled. Should 2 or more subjects in either cohort experience DLT as defined above, the study will be stopped pending review and discussion with FDA.

STOPPING RULES

The occurrence of any of the following events (regardless of suspected causal associations) during or after the administration of AAV2-hAADC would result in the halting of study enrollment and notification of the DSMB, FDA, and IRB:

- Any significant procedural deviation or violations, e.g. dosing error, equipment failure
- Any symptomatic intra-cerebral hemorrhage or stroke that results in a significant new neurologic deficit that persists one month following surgery
- Any central nervous system infections related to study interventions
- Dyskinesias severe enough to require ICU admission for greater than 30 days
- Any death

Once a stopping rule is reached, the trial would be suspended (i.e., cessation of AAV2-hAADC administration to any subjects) pending a comprehensive safety review by the DSMB. Triggering of any Stopping Rule will prompt notification to FDA, IRB, NIH Office of Biotechnology, and the Institutional Biosafety Committee (IBC).

Additional Stopping Rules may be developed if unexpected serious adverse events (SAE) with likely related to AAV2-hAADC delivery, including delivery procedure, appear during the study.

Events that do not clearly meet the above criteria may be submitted to the DSMB, at the discretion of the study investigators, for independent review.

16 SAMPLE SIZE CALCULATIONS AND DATA ANALYSIS

This is an open-label safety study that has not been designed as a powered efficacy study. Statistical analysis will be performed on quantifiable measures of clinical responses to treatment by comparing pre- and post-operative assessments, and analyzing any differences between the two dose cohorts.

16.1 Sample Size

The number of subjects is based on the desire to gain adequate safety and preliminary clinical outcome information to support future work. Inferential statistical hypothesis testing is not the primary intent of the study. It is judged that the selected sample size, based on previous animal experience and empiric criteria, will provide acceptable clinical validity for the study objectives.

Previous Phase 1 studies involving innovative surgical and medical interventions for rare CNS disorders have historically enrolled similar numbers of subjects.

16.2 Data Analysis

Analysis of the study data will primarily be tabular, graphical and descriptive, with a view to elucidating the time course and pattern of responses to AAV2-hAADC treatment and thoroughly exploring the antecedents of any observed adverse effects of therapy. Particular attention will be paid to verifying that all subjects enrolled satisfy the stated inclusion criteria, and on checking for any protocol violations. Statistical analysis will be performed on quantifiable measures of clinical responses to treatment by comparing pre- and post-operative assessments, and analyzing any differences between the two dose cohorts.

Characteristics of the surgical procedure such as accuracy of cannula placement, number of cannula passes, any events during infusion such as reflux or non-targeted delivery will be analyzed. Coverage of target structures will be measured on the MR images acquired during the CED procedure. Calculations will be made of the total volume of gadoteridol distribution, percentage covered by gadoteridol, and percentage of gadoteridol distribution contained within the target structures.

16.3 Safety Analysis

Safety data will be summarized for the total study population and the pooled safety data will be further broken down by the dose level. The disposition of the patients will be summarized by tabulating the number of screened, completed, and discontinued patients. The reasons for premature discontinuations

will be tabulated. The extent of exposure to the study treatment will be summarized by tabulating the number of patients being exposed to each dose level.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The treatment-emergent AEs (TEAEs), i.e., events which start or worsen during the study treatment will be summarized by body system and preferred term. In addition, separate summaries will be provided for TEAEs by severity and relationship to study drug, as well as adverse events leading to study drug discontinuation and serious adverse events. The tolerability will be assessed by number of patients having DLTs and with premature discontinuations of study treatment.

The other safety analyses include the evaluation of safety laboratory tests, vital signs and brain imaging. The safety laboratory tests and vital signs will be evaluated by summarizing the changes from baseline with descriptive statistics and by tabulating the number of patients with abnormal values. The evaluation of the brain imaging is based on post-operative MRI and/or computed tomography (CT) (with contrast if clinically indicated) findings.

16.4 Efficacy Analysis

For the evaluation of the efficacy, there will be two primary clinical outcome measures:

- Motor Function, as assessed by the Gross Motor Function Measure (GMFM-88). The total score will be derived as an unweighted average of the 5 dimension scores: lying and rolling (17 items); sitting (20 items); crawling and kneeling (14 items); standing (13 items) and walking, running, and jumping (24 items). Each dimension score will be defined as % of maximum score for the dimension in question.
- Frequency of motor behaviors, as measured by a Symptom Diary: each recorded episode will be classified as mild, moderate or severe. The area under the curve (AUC) of the diary symptoms will be used as the endpoint. The AUC will be calculated for each study month as a sum of duration of symptoms (hours) multiplied by the severity (0-3) of the symptom in question. The endpoint is the change from baseline (average of 3 months preceding the baseline) to 1 year (average of 3 months preceding the visit at Month 12).

The secondary analyses of the primary endpoints include the evaluation of the data at time points other than 1 year. In addition, the following endpoints will be evaluated as secondary analyses:

- Evaluation of each of the 5 GMFM-88 dimension scores separately.

- Evaluation of the Symptom Diary as total number of episodes, total duration of episodes and distribution of the severity scores.

All data collected during the study will be used for the evaluation of the clinical outcome measures. The evaluation will be focused on the following comparisons:

- Change from baseline to one year in all patients treated with the selected dose level (primary comparison). However, if no dose-response is seen, both dose levels will be included in the primary comparison.
- Difference in change from baseline to one year between the patients treated with the selected dose level and the other dose level used.

In addition to the comparisons defined above, efforts will be made to compare the changes seen in the present study to natural progression of the disease as assessed in external natural history studies. These comparisons may involve comparison of the changes between the treated patients from the present study and untreated patients from a separate natural history study, using endpoints derived from the elements of the primary outcome measures. The definition of these endpoints depends on the availability of the natural history data.