Official Title: Phase I/IIa Gene Transfer Clinical Trial for Variant Late Infantile Neuronal Ceroid Lipofuscinosis, Delivering the CLN6 Gene by Self-Complementary AAV9

NCT Number: NCT02725580

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CLINICAL STUDY PROTOCOL

PHASE I/IIA GENE TRANSFER CLINICAL TRIAL FOR VARIANT LATE INFANTILE NEURONAL CEROID LIPOFUSCINOSIS, DELIVERING THE *CLN6* GENE BY SELF-COMPLEMENTARY AAV9

Protocol Number: AT-GTX-501-01

Version 17.0: 20 May 2020

(replaces Version 16.0: 4 March 2020)

US IND Number: 16854

Study Treatment: AT-GTX-501

Sponsor
Amicus Therapeutics, Inc.
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SIGNATURE PAGE

This clinical study protocol was subject to critical review and has been approved by Amicus Therapeutics (Amicus).

The information it contains is consistent with the following:

- The current benefit-risk evaluation of AT-GTX-501
- The moral, ethical, and scientific principles governing clinical research, as set forth in the current version of the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in the US Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312, and in the International Conference on Harmonization (ICH) GCP E6 guidelines.

Sponsor:

The investigator will be supplied with details of any significant or new findings related to treatment with AT-GTX-501.

Date: May 20, 2020 Signature: PPD

PPD MD, PhD
PPD Clinical Research
Amicus Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for AT-GTX-501. I confirm that I have read this clinical study protocol. I understand it and agree to conduct the study as outlined. I will work according to the moral, ethical, and scientific principles governing clinical research, as set forth in the current version of the Declaration of Helsinki and the principles of GCP described in the US CFR Parts 50, 54, 56, and 312, and in the ICH GCP E6 guidelines. I will also work in accordance with applicable local requirements.

Investigator:

Date: _____ Signature: _____

PPD MD

Nationwide Children's Hospital

PROCEDURES IN CASE OF EMERGENCY

Table 1: Contact Information for Serious Adverse Event Reporting

Role	Contact Information
Reporting of serious adverse events	**Primary method of contact:** Safety FAX number: + 1 866-422-1278 If fax is unsuccessful, please use: Safety email address: safetyreporting@amicusrx.com
Inquiries related to serious adverse event reporting	PPD MD PPD Global Head of Drug Safety Amicus Therapeutics Office number: PPD Mobile number: PPD

2. SYNOPSIS

Name of Sponsor: Amicus Therapeutics (Amicus)		
Name of Study Treatment: AT-GTX-501		
Name of Active Ingredient: scAAV9 containing the human *CLN6* gene		
Study Number: AT-GTX-501-01	**Phase:** I/IIa	**Country:** US
Title of Study: Phase I/IIa Gene Transfer Clinical Trial for Variant Late Infantile Neuronal Ceroid Lipofuscinosis, Delivering the *CLN6* Gene by Self-Complementary AAV9		
Study Center: Nationwide Children's Hospital, Columbus, Ohio		
Principal Investigator: PPD MD		
Studied Period (years): First subject, first visit: First Quarter 2016 Estimated date last subject completed: Fourth Quarter 2021		
Objectives: **Primary:** The primary outcome for this clinical study is safety. This is evaluated based on dose-limiting toxicity (DLT), defined as any unanticipated adverse event (AE) that is related to AT-GTX-501 (events assessed by the investigator as definitely, probably, or possibly related) and is Grade 3 or higher, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (published 28 May 2009). **Secondary and Exploratory:** The secondary and exploratory outcome measures are to evaluate the potential for prolonged survival or maintenance of motor, language, visual, and cognitive function. The outcome measures include the Hamburg (scale), the Unified Batten Disease Rating Scale (UBDRS), brain magnetic resonance imaging (MRI), cognitive and language evaluations, the Pediatric Quality of Life™ (PedsQL) inventory, ophthalmologic examinations, and long-term monitoring electroencephalograms. The primary efficacy outcome will be the Hamburg Motor and Language scores.		
Study Design and Methodology: AT-GTX-501 is a gene transfer product intended for patients with variant late infantile neuronal ceroid lipofuscinosis associated with mutation(s) in the *CLN6* gene (vLINCL6 disease), a subset of patients with CLN6 Batten disease. In earlier development work, the code used for this product was scAAV9.CB.CLN6, further described as a self-complementary adeno-associated viral vector, serotype 9 (scAAV9) containing the human *CLN6* gene under the control of a hybrid promoter (a cytomegalovirus enhancer fused to the chicken-β actin promoter). This is an open-label, single-dose study of AT-GTX-501 administered by a single intrathecal injection. Safety and efficacy are evaluated over a 2-year period. The efficacy assessments in this study are to evaluate motor, language, visual, and cognitive function, as well as survival and other outcome measures. In Year 1, subjects are tested at baseline, receive AT-GTX-501 on Day 0, and return for visits on Days 7, 14, 21, and 30 (Visits 3 to 7), and then every 3 months for Visits 7 (Month 3) to 10 (Month 12). In Year 2, data are collected every 3 months. During the conduct of the study, the coronavirus disease 2019 (COVID-19) pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. Therefore, remote visits were implemented per health authority guidance. These contingency measures are planned to be followed until resolution of COVID-19 related issues specific to the individual subject.		

Unscheduled visits may occur if the investigator determines that they are necessary. Following the current study, there is a long-term follow-up study in which data will continue to be collected (Study AT-GTX-501-02).

Number of Subjects (Planned): Approximately 13

Diagnosis: variant late infantile neuronal ceroid lipofuscinosis (disease)

Criteria for Inclusion:

1. Diagnosis of vLINCL6 disease determined by genotype available at screening (by a College of American Pathologists/Clinical Laboratory Improvement Amendments [CAP/CLIA]-certified laboratory [or a non-US laboratory with an equivalent national accreditation/certification])
2. A score of ≥ 3 on the quantitative clinical assessment of the Hamburg motor-language aggregate score at screening
3. Aged ≥ 1 year
4. Ambulatory or able to walk with assistance

Criteria for Exclusion:

1. Presence of another inherited neurologic disease, eg, other forms of Batten disease (also known as neuronal ceroid lipofuscinosis) or seizures unrelated to vLINCL6 disease (Subjects with febrile seizures may be eligible at discretion of the investigator.)
2. Presence of another neurological illness that may have caused cognitive decline (eg, trauma, meningitis, hemorrhage) before screening
3. Active viral infection (includes HIV or serology positive for hepatitis B or C)
4. Has received stem cell or bone marrow transplantation for vLINCL6 disease
5. Contraindications for intrathecal administration of the product or lumbar puncture, such as bleeding disorders or other medical conditions (eg, spina bifida, meningitis, or clotting abnormalities)
6. Contraindications for magnetic resonance imaging (MRI) scans (eg, cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain)
7. Episode of generalized motor status epilepticus within 4 weeks before the gene transfer visit (Visit 2)
8. Severe infection (eg, pneumonia, pyelonephritis, or meningitis) within 4 weeks before the gene transfer visit (Visit 2) (Enrollment may be postponed.)
9. Has received any investigational medication within 30 days before the gene transfer visit (Visit 2)
10. Anti-AAV9 antibody titers > 1:50 as determined by ELISA (enzyme-linked immunosorbent assay)
11. Has a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise the subject's ability to comply with the protocol-required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability
12. Pregnancy any time during the study (Any female subject judged by the investigator to be of childbearing potential will be tested for pregnancy.)
13. Abnormal laboratory values from screening considered clinically significant (gamma-glutamyl transferase > 3 times the upper limit of normal, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.8 mg/dL, hemoglobin < 8 or > 18 g/dL, white blood cell count > 15,000 per cmm)

14. Family does not want to disclose subject's study participation with primary care physician and other medical providers.
15. History of or current chemotherapy, radiotherapy, or other immunosuppression therapy within the 30 days preceding screening (Corticosteroid treatment may be permitted at the discretion of the investigator.)
16. Has 2 consecutive abnormal liver tests at screening (> 2 times the upper limit of normal). Liver enzymes will be re-tested once if abnormal upon initial screening.

Investigational Product, Dosage, and Mode of Administration:

AT-GTX-501 is delivered via a single intrathecal injection at a dose of 1.5×10^{13} vector genomes (as assessed by polymerase chain reaction [PCR] and relative to a supercoiled standard), after being premixed with Omnipaque™ contrast.

Study Duration: 2 years (for each individual subject)

Reference Therapy, Dosage, and Mode of Administration: Not applicable

Safety Assessments:

- AEs
- Clinical safety laboratory assessments (including serum chemistry, hematology, and urinalysis)
- Immunogenicity assessments
- 12-lead electrocardiograms
- Concomitant Medications
- Neurological examinations
- Physical examinations (including weight, height, and vital signs)

Efficacy Assessments:

- Hamburg scale
- UBDRS
- Cognitive and language evaluations
- Brain MRIs
- Ophthalmologic examinations
- Ocular coherence tomography (OCT)
- electroencephalograms (EEGs)
- PedsQL
- Derived measures (eg, Survival, analyses relative to historical control or interview data)

Statistical Methods:

This is a phase I/IIa study, inclusive of safety and efficacy. The primary outcome (safety) will be evaluated based on the development of DLTs. The secondary and exploratory outcome measures are to evaluate the potential for prolonged survival or maintenance of motor, language, visual, and cognitive function. The primary efficacy outcome will be the Hamburg Motor and Language scores.

Descriptions of all endpoints and their planned analyses will be detailed in the Statistical Analysis Plan (SAP). Baseline is generally defined as the measure immediately preceding receipt of AT-GTX-501.

3. TABLE OF CONTENTS AND LIST OF TABLES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in the body of this study protocol. Abbreviations used in tables are defined in their respective footnotes.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
AAV9	adeno-associated virus, serotype 9
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT-GTX-501	a gene transfer product containing the human *CLN6* gene
CFR	Code of Federal Regulations
CLN6	the human and nonhuman primate gene associated with vLINCL6 disease and other Batten disease variants, such as adult onset Kufs Type A disease (in mice and other animal models: *Cln6*)
Cln6^{nclf}	a mouse model of CLN6 Batten disease
CLN6 protein	the protein product of the *CLN6* gene, ceroid lipofuscinosis neuronal protein 6
COVID-19	coronavirus disease 2019
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot (assay)
EUA	examination under anesthesia
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
ICF	informed consent form
ICH	International Conference on Harmonization
ICV	intracerebroventricular
IFN-γ	interferon gamma
IRB	Institutional Review Board
MRI	magnetic resonance imaging
NCH	Nationwide Children's Hospital
NCL	neuronal ceroid lipofuscinosis
NHP	nonhuman primate
OCT	ocular coherence tomography
PCR	polymerase chain reaction (when quantitative: qPCR)
PCS	potentially clinically significant
PedsQL	Pediatric Quality of Life™ (inventory)
PICU	pediatric intensive care unit
SAE	serious adverse event
SAP	statistical analysis plan
sc	self-complementary
scAAV9.CB.CLN6	a gene transfer product containing the human *CLN6* gene Note: Amicus code for this product is 'AT-GTX-501.'
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UBDRS	Unified Batten Disease Rating Scale
vg	vector genomes
vLINCL6 disease	variant late infantile neuronal ceroid lipofuscinosis associated with mutation(s) in the *CLN6* gene

5. INTRODUCTION

5.1. Background

Batten diseases represent a group of heterogeneous, lysosomal disorders characterized by pathological intracellular accumulation of ceroid lipofuscin in neurons and other cell types. Collectively, although the disorder is most commonly known as Batten disease, it is also referred to as neuronal ceroid lipofuscinosis (NCL). The disorder is classified based on the genetic mutation. There are 14 different phenotypes with 13 causative genes identified (Schulz, Kohlschutter et al. 2013; Mole, Anderson et al. 2019). Of the recognized genes in which mutations may cause a Batten disease phenotype, *CLN6* gene mutations have been associated with both childhood (late infantile) and later-onset phenotypes.

In general, Batten diseases as a group are progressive degenerative diseases that primarily affect the brain and the retina. Clinically, individuals with variant late infantile neuronal ceroid lipofuscinosis associated with mutation(s) in the *CLN6* gene (vLINCL6 disease) typically present with their first signs or symptoms before 5 years of age. These may include language delay, cognitive regression, ataxia, and pyramidal and extrapyramidal signs. Subjects with vLINCL6 disease experience a decline in visual perception early in the progression of the disease. Most children lose ambulation within 4 years from disease onset (Canafoglia, Gilioli et al. 2015). A report by Sharp and colleagues describes language delay by 2 to 3 years of age, and seizures, ataxia and myoclonus, and visual failure at 5 to 6 years of age (Sharp, Wheeler et al. 2003). Therefore, the clinical presentation of the disease can be variable. Death usually occurs between 5 and 12 years of age but may occur later. Sometimes, cases can be protracted and may present at a later age, perhaps referred to as the 'adult variant' or Kufs Type A (Arsov, Smith et al. 2011). All Batten diseases, regardless of the causative gene, result in loss of cognitive skills at some stage of the disease.

Mutations in the *CLN6* gene cause vLINCL6 disease; the *CLN6* gene encodes ceroid lipofuscinosis neuronal protein 6 (CLN6 protein). The CLN6 protein is a transmembrane protein in the endoplasmic reticulum (Gao, Boustany et al. 2002). When the CLN6 protein is absent or mutated, lysosomal function is altered. This results in abnormal accumulation of ceroid lipofuscin, which would normally be degraded in the lysosome. In the central nervous system (CNS), intracellular accumulation of these materials results in early destruction of neural cells (Kurze, Galliciotti et al. 2010).

Currently, there is no cure or treatment for vLINCL6 disease other than symptomatic and supportive care. Therefore, a clinical study of AT-GTX-501, a gene transfer product containing the human *CLN6* gene, will provide information on the potential of gene transfer in treating patients with vLINCL6 disease.

5.2. Study Treatment

Subjects in this study will receive AT-GTX-501, further described as a self-complementary adeno-associated viral vector, serotype 9 (scAAV9) containing the human *CLN6* gene under the control of a hybrid promoter (a cytomegalovirus enhancer fused to the chicken-β actin promoter).

5.3. Study Rationale

5.3.1. Overview of Study Design

This clinical study is an open-label, single dose study in which the study treatment, AT-GTX-501, will be delivered by a single intrathecal injection into the lumbar spinal cord region of young pediatric subjects with vLINCL6 disease. The rationale for the dose and route of administration are described in Section 5.3.3. The study design is further described in Section 7.1.

5.3.2. Rationale for Study Treatment

This is the first clinical study of AT-GTX-501. The target for this gene transfer study is vLINCL6 disease. The *CLN6* gene will be transferred using scAAV9 carrying the human *CLN6* gene under control of a hybrid cytomegalovirus enhancer/chicken-β-actin promoter (AT-GTX-501). The specific scAAV9 viral vector was chosen based on both nonclinical studies and its safety in human subjects as seen in a Phase I clinical study for infants with type I spinal muscular atrophy (Mendell, Al-Zaidy et al. 2017).

The rationale for this approach is based on studies of the natural history of vLINCL6 disease, its genetic cause, and its lack of therapies.

Pathogenic mutations in the *CLN6* gene cause vLINCL6 disease, which is a severe neurodegenerative disorder leading to dementia, epilepsy, motor impairment, and visual loss. The age of disease onset varies between 18 months and 8 years, but the outcome is fatal in all cases, typically leading to death within the first 15 years of life. The CLN6 protein is a transmembrane protein located in the endoplasmic reticulum (Gao, Boustany et al. 2002). As with many other Batten disease-causing gene products, the exact function of the CLN6 protein is still unknown. This makes it difficult to develop effective drug-based therapies for this devastating disorder, as the affected pathways that need to be targeted are poorly understood. Moreover, the ubiquitous expression of the CLN6 protein and the sensitivity of various neuronal cell types to its malfunction requires widespread targeting of treatment throughout the CNS and potentially other organs of the body. The pathogenic *CLN6* mutations described to date are thought to cause a reduced abundance or functionality of the protein (Heine, Koch et al. 2004). Therefore, strategies aiming to restore CLN6 protein expression and/or function are under investigation as therapeutic approaches. Current treatments are only palliative in nature and no therapies exist to treat the underlying cause of vLINCL6 disease.

Preceding nonclinical and clinical safety studies have shown scAAV9-mediated gene transfer to be safe and well-tolerated in mice, cats, monkeys, and in human subjects in clinical studies (Foust, Salazar et al. 2013; Bucher, Dubreil et al. 2014; Meyer, Ferraiuolo et al. 2015; Mendell, Al-Zaidy et al. 2017).

5.3.3. Rationale for Dose and Route of Administration

The clinical dose of 6 x 10^{13} vector genomes (vg), based on polymerase chain reaction (PCR) and relative to a supercoiled standard, is based on a cerebrospinal fluid (CSF)-volume based increase to the dose in young cynomolgus macaques that achieved efficient brain and spinal cord transduction via CSF delivery at a lower dose of viral vector (2 x 10^{13} vg). The dose of

6 x 10^{13} vg is based on the maximal increase of CSF volume of 2- to 3-fold from young to adult cynomolgus macaques.

The delivery route is based on the transduction pattern observed in nonclinical studies, in which intrathecal administration followed by short-term (10 to 15 minutes) placement of the subject in the Trendelenberg position resulted in the most efficient targeting throughout all brain regions. The delivery of AT-GTX-501 directly into the CSF also allows for reduction of the amount of the scAAV9 vector by a factor of 10 (relative to peripheral administration), while also achieving equal distribution and efficacy throughout the CNS. The delivery into the CSF also results in reduced scAAV9 vector loads in major peripheral organs, such as the liver, thereby further optimizing the safety profile of AT-GTX-501.

5.4. Summary of Key Nonclinical Results

The below nonclinical results are especially pertinent to the clinical development program for AT-GTX-501 for the treatment of vLINCL6 disease:

- Initial nonclinical evaluations of the safety of delivering a *CLN6* transgene were performed in a toxicology study using AT-GTX-501 in mice that received an intracerebroventricular (ICV) injection at a dose of 3.3×10^{13} vg/kg. This dose allowed efficient targeting of the brain and spinal cord. Doses that led to similar targeting of the brain and spinal cord were then used in nonhuman primates (NHPs). These nonclinical studies were the foundation for the dose selection in this Phase I/IIa treatment study.
- Initial evaluations of efficacy for AT-GTX-501 were performed using the mouse model of CLN6 Batten disease (*Cln6*^{nclf}). A single AT-GTX-501 ICV injection (dose of 3.3×10^{13} vg/kg) was sufficient to induce widespread expression of human CLN6 protein throughout the CNS of *Cln6*^{nclf} mice. Untreated *Cln6*^{nclf} mice show a hallmark of CLN6 Batten disease, accumulation of ceroid lipofuscins throughout the cerebral cortex. However, at 1 month of age, *Cln6*^{nclf} mice that were injected with AT-GTX-501 at postnatal day 2 did not show this abnormal accumulation of ceroid lipofuscin (referred to as autofluorescent storage material [ASM]) and ASM levels were comparable to those seen in wild-type mice. Furthermore, a behavioral test (rotorod motor performance assay) in these mice showed that AT-GTX-501-injected *Cln6*^{nclf} mice performed significantly better than vehicle-injected *Cln6*^{nclf} mice.
- Studies in young NHPs (cynomolgus macaques) demonstrated efficient brain and spinal cord transduction, achieved via CSF delivery at a lower dose (2×10^{13} vg) than the 3.3×10^{13} vg that was required for mice. Subsequently, accounting for increased CSF volume with increased age, studies in older NHPs identified an adjusted dose of 6×10^{13} vg for the maximal 3-fold increase in CSF volume. Injection of AT-GTX-501 in older NHPs did not induce major changes in serum chemistry or hematology up to 2 months after injection, and no organ pathology was found after euthanasia.
- Overall, there were no significant findings or safety concerns raised in the nonclinical studies at doses resulting in widespread and efficient brain and spinal cord transduction (mice and NHPs).

- Safety of administering an scAAV9 vector to humans is also inferred from a spinal muscular atrophy gene transfer study (Mendell, Al-Zaidy et al. 2017) in which the only adverse events (AEs) observed and considered related to treatment were transient and asymptomatic elevations in aminotransferase levels.

5.5. Study Population

This study will include approximately 13 subjects with vLINCL6 disease. All subjects are required to have a documented mutation in the *CLN6* gene.

At the time of entry into Study AT-GTX-501-01, subjects are required to have a minimum baseline motor-language aggregate score on the Hamburg scale (see Section 11.1) of ≥ 3. Also, subjects are required to meet an age requirement of being ≥ 1 year of age.

Eligible subjects need to meet other exclusionary requirements, such as lack of certain concomitant diseases or illnesses, no previous receipt of certain investigational or other treatments, and lack of contraindications for procedures specified by this protocol.

6. OBJECTIVES AND PURPOSE

This study is a Phase I/IIa clinical study, inclusive of safety and efficacy.

6.1. Primary Objective

The primary outcome for this clinical study is safety. This is evaluated based on an outcome measure of dose-limiting toxicity (DLT), defined in Section 12.2.1.5 as any unanticipated AE that is related to AT-GTX-501 (events assessed by the investigator as definitely, probably, or possibly related) and is Grade 3 or higher, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (published 28 May 2009).

6.2. Secondary Objectives

The secondary and exploratory outcome measures are to evaluate the potential for prolonged survival or maintenance of motor, language, visual, and cognitive function. The outcome measures include the Hamburg (scale), the Unified Batten Disease Rating Scale (UBDRS), brain magnetic resonance imaging (MRI), cognitive and language evaluations, the Pediatric Quality of Life™ (PedsQL) inventory, ophthalmologic examinations, and long-term monitoring electroencephalograms. The primary efficacy outcome will be the Hamburg Motor and Language scores.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a study in subjects with vLINCL6 disease who receive a single intrathecal administration of AT-GTX-501.

Safety and efficacy are evaluated over a 2-year period. The efficacy assessments in this study are to evaluate motor, language, visual, and cognitive function, as well as survival and other outcome measures. In Year 1, subjects are tested at baseline, receive AT-GTX-501 on Day 0, and return for visits on Days 7, 14, 21, and 30 (Visits 3 to 6), and then every 3 months for Visits 7 (Month 3) to 10 (Month 12). In Year 2, data are collected every 3 months.

During the conduct of the study, the COVID-19 pandemic emerged and impeded the conduct of site visits and laboratory testing due to quarantines, travel restrictions, and risk of infection. Therefore, remote subject visits were implemented per health authority guidance. The overall study design and timing of assessments is unchanged during the period of time in which the investigator will perform remote assessments. The Schedule of Assessments, Table 3 in Section 9.5, Description of Study Visits, continues to show the target timing and interval for data collection. Further details on the performance of remote visits are contained in the Remote Patient Visit Plan. These contingency measures are planned to be followed until resolution of COVID-19 related issues specific to the individual subject. Any assessment that cannot be performed will be a protocol deviation and recorded in the electronic case report form (eCRF) with the reason for protocol deviation as "COVID-19."

Following the current study, there is a long-term follow-up study in which data will continue to be collected (Study AT-GTX-501-02, see Section 9.6).

7.2. Number of Subjects

Approximately 13 subjects will be enrolled into this study.

7.3. Treatment Assignment

This is an open-label study and all subjects receive the same treatment.

7.4. Dose Adjustment Criteria

There are no dose adjustment criteria for this study. This is a one-time (single dose) treatment and dose adjustment is not applicable.

7.5. Criteria for Study Termination

Although there are no pre-defined stopping criteria for this study, safety data will be monitored throughout the study. An independent Data Safety Monitoring Board (DSMB [see Section 14.4]) can recommend pausing enrollment for reasons of safety. Study enrollment will be paused when 2 or more subjects experience a Grade 3 DLT (as defined in Section 12.2.1.5), if any subject experiences a Grade 4 DLT, or if any subject experiences any of the following:

- Death of any subject, irrespective of relation to AT-GTX-501

- Rapid neurological deterioration (outside of the anticipated decline that occurs with this disease); this may include, but is not limited to, paralysis, refractory seizures, or stroke
- Widespread inflammatory response with imaging or safety blood laboratory results that are not reversible and that correlate with a change in neurologic function or clinical status

The events will be reviewed by the DSMB, which will evaluate if the board recommends that the study be terminated early. If the decision is made to continue, the study will proceed according to Section 7.6.

Further, Amicus may terminate this study at any time after informing the investigator and relevant regulatory agencies. The US Food and Drug Administration (FDA) or other regulatory authorities may also instruct or recommend discontinuation or alteration of the study. Amicus will notify the investigator if the study is to be placed on hold, completed, or terminated.

7.6. Enrollment Frequency

For the initial 12 subjects, there was at least a 3-week interval between dosing of subjects to allow review of the safety data from 5 time points (Days 1, 2, 7, 14, and 21) prior to dosing of the next subject. Safety analyses were done by the investigator and the DSMB, as appropriate per Section 14.4, in time for decisions to be made about whether to continue enrollment.

Beyond the first 12 subjects, the DSMB will conduct routine meetings as per their charter (further described in Section 14.4).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all of the inclusion criteria and none of the exclusion criteria.

8.1. Subject Inclusion Criteria

1. Diagnosis of vLINCL6 disease determined by genotype available at screening (by a College of American Pathologists/Clinical Laboratory Improvement Amendments [CAP/CLIA]-certified laboratory [or a non-US laboratory with an equivalent national accreditation/certification])
2. A score of ≥ 3 on the quantitative clinical assessment of the Hamburg motor-language aggregate score at screening
3. Aged ≥ 1 year
4. Ambulatory or able to walk with assistance

8.2. Subject Exclusion Criteria

1. Presence of another inherited neurologic disease, eg, other forms of Batten disease (also known as NCL) or seizures unrelated to vLINCL6 disease (Subjects with febrile seizures may be eligible at discretion of the investigator.)
2. Presence of another neurological illness that may have caused cognitive decline (eg, trauma, meningitis, hemorrhage) before screening
3. Active viral infection (includes HIV or serology positive for hepatitis B or C)
4. Has received stem cell or bone marrow transplantation for vLINCL6 disease
5. Contraindications for intrathecal administration of the product or lumbar puncture, such as bleeding disorders or other medical conditions (eg, spina bifida, meningitis, or clotting abnormalities)
6. Contraindications for magnetic resonance imaging (MRI) scans (eg, cardiac pacemaker, metal fragment or chip in the eye, aneurysm clip in the brain)
7. Episode of generalized motor status epilepticus within 4 weeks before the gene transfer visit (Visit 2)
8. Severe infection (eg, pneumonia, pyelonephritis, or meningitis) within 4 weeks before the gene transfer visit (Visit 2) (Enrollment may be postponed.)
9. Has received any investigational medication within 30 days before the gene transfer visit (Visit 2)
10. Anti-AAV9 antibody titers > 1:50 as determined by ELISA (enzyme-linked immunosorbent assay)
11. Has a medical condition or extenuating circumstance that, in the opinion of the investigator, might compromise the subject's ability to comply with the protocol-required testing or procedures or compromise the subject's wellbeing, safety, or clinical interpretability

12. Pregnancy any time during the study (Any female subject judged by the investigator to be of childbearing potential will be tested for pregnancy.)
13. Abnormal laboratory values from screening considered clinically significant (gamma-glutamyl transferase [GGT] > 3 times the upper limit of normal, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.8 mg/dL, hemoglobin < 8 or > 18 g/dL, white blood cells > 15,000 per cmm)
14. Family does not want to disclose subject's study participation with primary care physician and other medical providers.
15. History of or current chemotherapy, radiotherapy, or other immunosuppression therapy within the 30 days preceding screening (Corticosteroid treatment may be permitted at the discretion of the investigator.)
16. Has 2 consecutive abnormal liver tests at screening (> 2 times the upper limit of normal). Liver enzymes will be re-tested once if abnormal upon initial screening.

8.3. Subject Withdrawal Criteria

There are no subject withdrawal criteria for this study.

8.4. Subjects with Concomitant Illness

At Visit 1, any illnesses present are to be captured as AEs and documented in the appropriate electronic case report form (eCRF). Any emergence or worsening of a concomitant illness during the study will be regarded as a treatment-emergent adverse event (TEAE) and will be reported in the AE eCRF.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Treatment

Gene transfer via AT-GTX-501 includes 3 key phases: the prophylactic administration of prednisolone/prednisone (Section 9.1.1), the administration of AT-GTX-501 (Section 9.1.2), and then monitoring in the pediatric intensive care unit (PICU) immediately post-gene transfer (Section 9.1.3).

9.1.1. Prophylactic Administration of Prednisolone/Prednisone

Subjects will be started on an oral dose of prophylactic prednisolone/prednisone (glucocorticoid) 1 day prior to gene transfer via AT-GTX-501. In most cases this will be prednisolone, 1 mg/kg/day with a maximum dose of 60 mg/day. Prednisone at the same dose is acceptable as well as a comparable glucocorticoid administered intravenously if it were to be required. The glucocorticoid is intended to serve as an immunosuppressive to dampen host immune response to AAV or transgene, which is an expected reaction following gene transfer.

Oral prednisone or prednisolone administration will continue after the gene transfer itself and will be tapered according to results from measuring AST, ALT, GGT, and bilirubin (total and fractionated [direct and indirect]) to assess liver function and from interferon gamma (IFN-γ) T-cell studies (enzyme-linked immunospot [ELISpot] assays) to assess immune response to AAV9 and CLN6 peptides in the following weeks.

- Post-gene transfer, at some time after Day 30, the subject's prednisone or prednisolone dose may begin to be tapered if (1) AST, ALT, GGT, and bilirubin results while on-steroid are not considered clinically significantly abnormal by the investigator, and if (2) ELISpot responses to both AAV9 and CLN6 peptides are negative or mildly positive per laboratory criteria. Tapering will proceed slowly, typically over 4 to 7 weeks.
  - Depending on the discretion of the investigator, the steroid dose may instead be increased (eg, to approximately 2 mg/kg/day). Accordingly, the subsequent tapering protocol would be prolonged; however, the guidelines for tapering as described above will be followed.
- At any point, if either the AST or ALT exceed > 2.5X the subject's Visit 1 (screening/baseline) values, and results are confirmed on a follow-up blood test within 3 days, the prednisone or prednisolone regimen will be maintained or increased (at the investigator's discretion) until the enzyme levels fall below the 2.5X elevation.

Based upon other studies, it is anticipated that oral prednisone or prednisolone administration will not exceed 120 days post gene transfer; regardless, testing of AST, ALT, GGT, and bilirubin is included at every site visit (at Days 7, 14, 21, and 30, at Months 3, 6, 9, and 12, and then every 6 months through Month 24). Additional assessments of AST, ALT, GGT, and bilirubin will be performed as needed; at a minimum these parameters will be measured and evaluated 1 to 2 weeks before initiating the planned final dose of steroid (ie, when tapering is almost complete) and 2 weeks after the final dose of steroid. During the period of COVID-19 contingency

measures, the sample collection and measurement of AST, ALT, GGT, and bilirubin may be performed locally rather than at the study site (see Remote Patient Visit Plan).

9.1.2. Administration of Study Treatment

The gene transfer infusion procedure will be done in the interventional radiology suite, under sterile conditions.

Prior to delivery of AT-GTX-501 the subject will be anesthetized by an experienced anesthesiologist. The choice of agents for anesthesia will be guided by the experience of the anesthesiologist, with careful monitoring during the procedure. Vital signs will be monitored throughout the procedure, including pulse oximetry, heart rate, blood pressure, temperature, and respiration rate. Information on concomitant medications, vital signs, and, if any occur, AEs will be recorded to be reported on the appropriate eCRF.

Preparation of AT-GTX-501 for administration:

- AT-GTX-501 is formulated in the Nationwide Children's Hospital (NCH) Investigational Pharmacy in 2.5 mL of Omnipaque™ (for further detail, see Section 10.4)
- AT-GTX-501, as prepared for administration with Omnipaque, is delivered to the procedure room in pre-labeled syringes sealed in double-sealed leak-proof bags and carried in a designated lockable cooler

Administration of AT-GTX-501:

- The subject will be placed in the lateral decubitus position
- Photograph(s) of the planned infusion site(s) are taken
- Under fluoroscopy guidance, an interventional radiologist will insert a lumbar puncture needle with stylet (a 22 GA Becton Dickinson™ [BD] spinal needle) into the L3-L4 or L4-L5 interspinous space, and then continue into the subarachnoid space
  - Subarachnoid cannulation will be confirmed with the flow of clear CSF from the catheter
- Prior to administration of AT-GTX-501, 5 mL of CSF will be removed for future analysis of such things as protein, glucose, cell count, and differential
- AT-GTX-501, as prepared for administration, will be injected directly into the subarachnoid space over 3 to 5 minutes
  - AT-GTX-501 will be administered to the subject within 8 hours of preparation
  - All subjects will receive via a 10 mL BD syringe (Luer-Lok™ Tip) a single dose of 1.5×10^{13} vg AT-GTX-501. This will be administered premixed with 2.5 mL of the contrast agent Omnipaque at a concentration of 180 mgI/mL of the contrast
- Following injection, subject will be placed in the Trendelenburg position, with their body tilted head-down for approximately 15 minutes

  - Use of the Trendelenburg position for approximately 15 minutes is used to promote distribution of the vector to areas of the upper spinal cord and brain (Meyer, Ferraiuolo et al. 2015)
- Photograph(s) of the infusion site are taken

9.1.3. Monitoring Immediately Following Gene Transfer

Each subject will be returned to their designated PICU bed following gene transfer. As done during the gene transfer procedure, information on concomitant medications, vital signs, and AEs will be recorded to be reported in the appropriate eCRF.

Each subject will be kept in the PICU for approximately 48 hours. During their admission to the PICU, the following procedures will be followed:

- Continued close monitoring of vital signs, with vital signs monitored every 15 minutes for 4 hours and every hour for the first 24 hours
- Continued monitoring and documentation of concomitant medications and all AEs/SAEs, including close monitoring of mental status

Subjects will be discharged based on the judgment of the investigator, including consideration of the following 4 criteria:

1. Afebrile
2. Absence of hypersensitivity reactions
3. Absence of meningismus, vomiting, or headache
4. Absence of clinically significant abnormal laboratory values

Before discharge, subjects' parents/caregivers will be provided standardized handouts that have been approved by the hospital with regard to monitoring for mental status changes.

9.2. Concomitant Medications and Therapies

There are no restrictions on concomitant medications during this study.

There are neither restrictions nor prescriptions for any non-drug therapies (eg, physical, occupational) or other procedures or accommodations (eg, wheelchair use) during the study. Site and primary care providers are to use best practices in providing support for subjects participating in the study.

See Section 12.1.2 for instructions on recording of concomitant medications, as well as non-drug therapies, other procedures, or accommodations.

9.3. Treatment Compliance

In this study a single intrathecal administration of study drug is performed; monitoring of treatment compliance is not applicable.

9.4. Randomization and Blinding

Not applicable. This is an open-label study.

9.5. Description of Study Visits

9.5.1. Visit Schedule

Before completion of any study-specific procedures, a written informed consent will be obtained (Section 16.4). All study assessments/procedures are to be conducted by the investigator and/or a suitably qualified delegate.

As shown in the Schedule of Assessments (Table 3), following Visit 1, all visits are to occur within a window of ± 2 days for Visits 3 through 6 and ± 30 days for Visits 7 through 14.

Each site visit will span at least 2 days and is expected to require an overnight stay, thus also necessitating completion of hospital registration procedures for each visit. The order of performance of assessments is at the discretion of the investigator, who will consider assessment timing to ensure that fatigue from previous assessments would not be expected to impact the outcome of the assessment (particularly following any examinations under anesthesia [EUAs], as described in Section 11.9). From visit to visit, attempts will be made to perform relevant assessments in the same general order and by the same rater.

Remote subject visits will occur until resolution of COVID-19 related issues specific to the individual subject (see Remote Patient Visit Plan).

Table 3: Schedule of Assessments

vLINCL6 disease Study Procedures	Screening	Gene Transfer (Visit 2)				Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Visit 9[a]	Visit 10[a]	Visit 11[a]	Visit 12[a]	Visit 13[a]	Visit 14[a]
	Day -30 to -2	Day -1	Day 0	Day 1	Day 2	Day 7	Day 14	Day 21	Day 30	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Visit window						±2d	±2d	±2d	±2d	±30d	±30d	±30d	±30d	±30d	±30d	±30d	±30d
Informed consent (Section 16.4)	X																
Chest X-ray (Section 12.1.3)	X																
Medical history (Section 12.1.1)	X																
Interview for interim assessment of subject status and function (Section 11.3)														X		X	
Interview re: historical subject status and function (Section 11.3)																	X
PedsQL (Section 11.8)	X												X				X
Physical exam, including vitals (Section 12.1.3)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological exam (Section 11.5)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lumbar puncture (Section 9.1.2, Section 12.1.5.5)			X														X
Gene transfer (Section 9.1.2)			X														
Brain MRI, OCT, Fundus photography (Section 11.9)	See Section		X										X				X

Table 3: Schedule of Assessments (Continued)

vLINCL6 disease Study Procedures	Screening	Gene Transfer (Visit 2)				Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Visit 9[a]	Visit 10[a]	Visit 11[a]	Visit 12[a]	Visit 13[a]	Visit 14[a]
	Day -30 to -2	Day -1	Day 0	Day 1	Day 2	Day 7	Day 14	Day 21	Day 30	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Visit window						±2d	±2d	±2d	±2d	±30d	±30d	±30d	±30d	±30d	±30d	±30d	±30d
Infusion site photographs (Section 9.1.2, Section 12.1.3)	X	X	X	X	X	X	X	X	X								
Hamburg with video and UBDRS (Section 11.1, Section 11.2)	X								X	X	X	X	X	X	X	X	X
Long-term monitoring EEG (Section 11.4)	X												X				X
Ophthalmologic exams (Section 11.7)	X								X		X		X		X		X
Cognitive and language evals (Section 11.6)	X										X		X				X
Electrocardiogram (Section 12.1.4)	X												X				X
Safety labs (blood and urine) Section 12.1.5.1)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Additional assessments of AST, ALT, GGT, and Bilirubin (Section 12.1.5.1)			As needed as per Section 9.1.1. At a minimum these will be measured and evaluated 1 to 2 weeks before initiating the final dose of steroid (during down-tapering) and 2 weeks after the last dose of steroid. If necessary, these may be performed locally.														
HIV and Hep B or C (Section 12.1.5.1)	X																

Table 3: Schedule of Assessments (Continued)

vLINCL6 disease Study Procedures	Screening	Gene Transfer (Visit 2)				Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8[a]	Visit 9[a]	Visit 10[a]	Visit 11[a]	Visit 12[a]	Visit 13[a]	Visit 14[a]
	Day -30 to -2	Day -1	Day 0	Day 1	Day 2	Day 7	Day 14	Day 21	Day 30	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Visit window						±2d	±2d	±2d	±2d	±30d	±30d	±30d	±30d	±30d	±30d	±30d	±30d
Immunology labs (Section 12.1.5.3)	X					X	X	X	X	X	X	X	X		X		X
Viral shedding samples (Section 12.1.5.4)	X					X	X	X	X	X	X	X	X		X		X
Adverse events (Section 12.2)																	
Concomitant medications, non-drug therapies, and other procedures or accommodations (Section 12.1.2)																	

Abbreviations: EEG = electroencephalogram; Hep B or C = Hepatitis B or C; HIV = human immunodeficiency virus; labs = laboratory assessments; MRI = magnetic resonance imaging; OCT = ocular coherence tomography; PedsQL = Pediatric Quality of Life (inventory); UBDRS = Unified Batten Disease Rating Scale

[a] Remote visits are planned to be followed until resolution of COVID-19 related issues specific to the individual subject. As per the Remote Patient Visit Plan, AEs and concomitant medications review, physical and neurological examinations, PedsQL assessments, Hamburg scale assessment, and UBDRS assessment will be performed during remote visits. Subjects may have samples collected at a local laboratory for the clinical safety laboratory assessments. See Remote Patient Visit Plan for a detailed description of remote assessments.

9.5.2. Unscheduled Visits

Unscheduled visits can be performed at any time at the investigator's discretion. At the discretion of the investigator, any safety or efficacy assessment may be performed at an unscheduled visit. Information collected is to be captured in the subject's source documents and on the appropriate eCRFs.

9.5.3. Early Termination Visit

All subjects will be encouraged to remain in the study until completion. However, any subject may withdraw consent and discontinue from the study at any time. In any such cases, the date of subject's withdrawal and the primary reason for discontinuation are to be recorded in the source documents and in the eCRF. The investigator is to make every effort to contact subjects who are lost to follow-up and every effort to schedule, as appropriate, a site visit, a remote visit/phone interview (as per Section 11.3), or an early termination (ET) visit, regardless of the time period since any previous data collection. Attempts to contact subjects who are lost to follow-up (eg, times and dates of attempted telephone contact, documentation of a registered letter) are to be recorded in the subject's source documents.

Any discontinuing subject will be requested to complete an ET visit, as shown in the Schedule of Assessments (Table 3).

9.6. Long-term Monitoring Following Gene Transfer

As indicated by the draft US guidance (FDA 2018), adeno-associated viral vectors have a very low probability of gene transfer-related delayed AEs. Short-term safety will be evaluated over a 2-year period that incorporates the active phase of the current protocol. Following the current study, subjects will be asked to transfer to a long-term follow-up study (Study AT-GTX-501-02) where follow-up data is planned to be collected for 13 years.

At the time of death, no matter what the cause, permission for an autopsy will be requested of subject's families. Subject's parents will be asked to advise their families of this request and of its scientific and medical importance.

10. STUDY TREATMENT MATERIALS AND MANAGEMENT

10.1. Study Treatment

AT-GTX-501 is manufactured in the Clinical Manufacturing Facility at NCH.

10.2. Packaging and Labeling

Each container of AT-GTX-501 will be labeled in conformance with regulatory requirements and where applicable, local laws.

10.3. Storage

AT-GTX-501 is stored at ≤ -60°C, in an area with restricted access. AT-GTX-501 is to be stored only at the site(s) listed on FDA Form 1572.

10.4. Preparation

Preparation of AT-GTX-501 for administration will be done by the NCH research pharmacist according to the Manual of Operating Procedures. Immediately prior to the transportation to the clinical setting, appropriate pre-mixing of AT-GTX-501 with Omnipaque will be completed by the pharmacy. Documentation of the mixing will be completed by the pharmacy following standard pharmacy protocol. AT-GTX-501 will be mixed and manipulated in polypropylene syringes.

Preparation of AT-GTX-501 will be performed aseptically in a Class II biological safety cabinet by pharmacy staff according to the Manual of Operating Procedures. AT-GTX-501, as prepared for administration, will be transferred from the pharmacy at room temperature to avoid the possibility of particle aggregation following product thaw. The AT-GTX-501-containing syringes will be delivered to the designated Interventional Radiology division at NCH. AT-GTX-501 will be delivered inside double-sealed leak-proof bags, carried in a designated lockable cooler at room temperature. AT-GTX-501 will be administered to the subject within 24 hours of removal from the freezer.

10.5. Administration

Administration of AT-GTX-501 is described in Section 9.1.2.

10.6. Accountability

Accountability records for supplies of AT-GTX-501 are to be maintained throughout the course of the study. Upon withdrawal of a vial, the Investigational Product Accountability Log will be recorded with the specific lot number and code of the vial. The study monitor will periodically check the supplies of AT-GTX-501 and verify the drug accountability logs are completed and maintained in the investigator study file.

10.7. Handling and Disposal

Handling of AT-GTX-501 will follow compliance standards for Biosafety Level 1 vectors following the NIH guidelines. Individuals manipulating AT-GTX-501 will be required to wear adequate personal protective equipment.

The site may not destroy AT-GTX-501, including used/partial vials of pure AT-GTX-501 or AT-GTX-501 mixed for administration but not used, unless Amicus has provided prior written approval.

11. ASSESSMENT OF EFFICACY

As appropriate, additional instruction regarding the performance of assessments will be provided in procedure manual(s). For consistency, efforts will be made to have each assessment for a particular subject performed by the same rater at all visits.

As per the Remote Patient Visit Plan, AEs/SAEs and concomitant medications review, physical and neurological examinations, PedsQL assessments, Hamburg scale assessment, and UBDRS assessment will be performed during remote visits. Subjects may have samples collected at a local laboratory for the clinical safety laboratory assessments.

11.1. Hamburg Scale

The Hamburg scale will be assessed at visits for Day -30 to Day -2 (baseline/screening), Day 30, and for Months 3, 6, 9, 12, 15, 18, 21, and 24. For each subject, videotaping is included at each time point. During the period of time in which COVID-19 contingency measures are in place, the Hamburg scale will be assessed during the remote visit (see Remote Patient Visit Plan).

The Hamburg scale was developed to document by rating motor, language, and visual functions in subjects with CLN2 Batten disease, and to collect their incidence of grand mal seizures (Steinfeld, Heim et al. 2002). The original Hamburg scale and modified versions of the motor and language domains of the Hamburg scale have been used to describe the natural history of CLN2 Batten disease (Nickel, Simonati et al. 2018) and to assess the effects of gene transfer (Worgall, Sondhi et al. 2008) and ICV enzyme replacement therapy for this disease (Schulz, Ajayi et al. 2018; Wyrwich, Schulz et al. 2018).

Although the Hamburg rating scale was originally developed for CLN2 Batten disease ("classic" late infantile disease), vLINCL6 is a related late infantile disease. Both CLN2 and vLINCL6 disease share a broadly similar clinical presentation that includes progressive decline in motor and cognitive abilities and seizures due to neuronal loss (Mole, Anderson et al. 2019), as well as vision loss and ataxia (Mink, Augustine et al. 2013). Previous authors have also described that patients with vLINCL6 disease may present with motor or language delay (with language delay by 2 to 3 years of age and seizures, ataxia/myoclonus, and visual failure at 5 to 6 years of age) and followed by death usually between 5 and 12 years of age (Sharp, Wheeler et al. 2003; Canafoglia, Gilioli et al. 2015). As such, the Hamburg scale is used to assess the effect of therapy in these subjects with vLINCL6 disease, and it or modified versions of the Hamburg scale are also being used to assess the natural rate of decline in untreated patients with vLINCL6 disease (NCT03285425) (Schulz, Simonati et al. 2015).

11.2. Unified Batten Disease Rating Scale

The UBDRS will be assessed at visits for Day -30 to Day -2 (baseline/screening), Day 30, and for Months 3, 6, 9, 12, 15, 18, 21, and 24. The UBDRS will be assessed at remote visits during the period of time in which COVID-19 contingency measures are in place (see Remote Patient Visit Plan).

The UBDRS was developed to monitor rate of progression in children with CLN3 Batten disease, also known as juvenile NCL (Marshall, de Blieck et al. 2005). Although the UBDRS scale was originally developed for CLN3 Batten disease, vLINCL6 disease has several similar clinical features. The version of the UBDRS used in this study collects data on the course of

extrapyramidal movement abnormalities and seizures. The scale also collects behavioral and capability assessments, as well as history relevant to vLINCL6 disease and scoring for global impression of symptom severity.

11.3. Interviews and Data Collection on Subject Status and Function

At up to 3 points during the study, interviews and data collection on subject status and function will be completed.

- For subjects who complete remote rather than onsite visits for Months 15 and/or Month 21, via an interview the investigator will solicit information based on appearance or disappearance of developmental milestones, activities of daily life, and/or results of assessments performed by other health care providers (eg, a local neurologist).
- At the Month 24 visit, an interview will be conducted for collection of the subject's history in regard to vLINCL6 disease prior to the subject's receipt of AT-GTX-501. Included will be a collection of the subject's family medical history in regard to vLINCL6 disease.

During these same conversations, safety-related information on AEs, concomitant medications, and non-drug therapies/procedures/accommodations will be solicited and recorded as appropriate (consistent with Section 12.1.2 and Section 12.4).

11.4. Electroencephalograms

A long-term (approximately 18 to 24 hours) monitoring electroencephalogram (EEG) will be performed at site visits on Day -30 to Day -2 (baseline/screening), Month 12, and Month 24. An EEG will not be performed during remote visits (see Remote Patient Visit Plan).

Each EEG is planned to include a portion while the subject is awake and a portion while the subject is sleeping (typically necessitating an overnight clinic stay).

These EEGs are to capture potential progression of encephalopathy, clinical seizures, and, if present, any epileptiform activity.

11.5. Neurological Examinations

A comprehensive neurological examination will be performed at all site visits. Refer to the Remote Patient Visit Plan for details of neurological examinations during remote visits.

11.6. Cognitive and Language Evaluations

Loss of cognitive and language function is a feature of vLINCL6 disease. Cognitive and language evaluations will be performed from Day -30 to Day -2 (baseline), and at Months 6, 12, and 24. Refer to the Remote Patient Visit Plan for details of cognitive and language evaluations during remote visits.

The evaluations will include the following:

- The Development Profile™-3

  - A patient-reported outcome tool (or caregiver checklist) used to screen children (birth through < 13 years of age) for developmental delays in 5 areas (physical, adaptive behavior, social-emotional, cognitive, and communication)

- The Mullen Scale of Early Learning
  - A scale designed to assess cognitive and motor ability in 5 areas (gross motor, visual reception, fine motor, expressive language, and receptive language) in infants and children (birth through 68 months of age [5 years, 8 months])
- Preschool Language Scales-5th Edition (PLS-5) (birth to 7 years, 11 months of age) OR, as appropriate for older children (5 years to 21 years, 11 months), the Clinical Evaluations of Language Fundamentals, 5th edition (CELF-5)
  - The PLS-5 is a comprehensive developmental language assessment with items that range from pre-verbal, interaction-based skills to emerging language to early literacy
  - The CELF-5 is a comprehensive battery of 16 stand-alone tests that provides a streamlined, flexible, and interactive approach to language assessment

Note that completion of standard cognitive and language evaluations is expected to be impacted in those subjects with progressive visual loss, another common feature of the disease. Also, although these scales do state an upper age limit for use, it may be appropriate to administer certain tests to cognitively impaired children who are chronologically older than the stated upper age limit but are functioning at a level equivalent to that of a younger child. Subjects who cross over into another age group and with sufficient development, as per the judgment of the study neuropsychologist, will be tested using the next age/function appropriate test(s). Completion of the appropriate assessments for an individual subject (potentially including assessments not listed above) will be as per the judgment of the study neuropsychologist.

11.7. Ophthalmologic Examinations

Ophthalmologic examinations will be performed at site visits for Day -30 to Day -2 (baseline), Day 30, and for Months 6, 12, 18, and 24. Ophthalmologic examinations will not be performed during remote visits (see Remote Patient Visit Plan).

These examinations will include visual acuity, refraction, confrontational visual field, external examination, ocular motility examination, pupil examination, intraocular pressure examination, slit lamp examination, and fundus examination, including fundus photographs as possible.

For assessment of visual acuity, variable levels of subject visual, cognitive, and verbal abilities are accounted for by the potential assessment approaches (refer to the procedure manual).

Additionally, special emphasis will be placed on monitoring changes in the retina, as described in Section 11.9.2.

11.8. Pediatric Quality of Life Inventory

The PedsQL inventory (both the family impact module and the parent report for children) will monitor the quality of life and will be performed at Visit 1 (Day -30 to Day -2;

baseline/screening) and at the visits for Months 12 and 24. Refer to the Remote Patient Visit Plan for details of the PedsQL assessment during remote visits.

The PedsQL is a modular approach to measuring health-related quality of life in healthy children and adolescents and in those with acute and chronic health conditions.

11.9. Examinations Performed Under Anesthesia

Following the baseline evaluations, examinations under anesthesia will only be performed in those subjects for whom separate consent for anesthesia was provided. All EUA will be performed during a single session under anesthesia. For EUAs, the preferred order of these assessments is brain MRI and then OCT; the lack of collecting one or more EUA will not be considered a protocol deviation. The possible collection of CSF at Month 24 (Section 12.1.5.5), which would also occur under anesthesia, is to follow the EUAs described in this section.

For both MRIs and OCTs and/or fundus photography, these will only be performed as possible and lack of anesthesia consent or incompletion of these assessments will not be considered a protocol deviation. If the OCT or fundus photography are able to be performed without anesthesia, they will be performed prior to Day 0 (at Visit 1) and the MRI will be the only assessment performed under anesthesia on Day 0 (at Visit 2, preceding the lumbar puncture to administer AT-GTX-501).

As needed, on a subject-by-subject basis, these EUAs may be discontinued and removed from later evaluations should the subject show signs or have a history of (1) not easily tolerating the procedure, (2) having any untoward effects or vital sign abnormalities during anesthesia, or (3) having any difficulty recovering following anesthesia.

During the period of time in which COVID-19 contingency measures are in place, remote visits will be conducted and examinations performed under anesthesia will not be performed.

11.9.1. Brain Magnetic Resonance Imaging

For those subjects who consented to anesthesia, brain MRI is to be performed at the visits for Day 0, Month 12, and Month 24. These MRIs will be utilizing a 3D MP-RAGE scan (a T1-weighted volumetric scan of the whole brain). In addition, a T2-weighted Gradient Echo and diffusion-weighted axial images will be recorded. These are to document progression of the disease, by using volumetric measures of the brain to capture the progression of atrophy. The MRIs will be discontinued from the study following a protocol amendment should 2 or more AEs occur related to the MRI procedure.

11.9.2. Ocular Coherence Tomography

When performed under anesthesia, OCT will be performed at the visits for Day 0 (Visit 2), Month 12, and Month 24. When possible, OCTs (and fundus photography) will be performed without anesthesia.

An OCT is a non-invasive method for obtaining a cross-sectional image of the layers of the retina, which may document flatting of the retina. At the time of the study ophthalmologist's evaluation of each OCT, a Weill Cornell score will be assigned. Retinal nerve fiber layer thickness and central foveal thickness will also be assessed via OCT results.

For those subjects for whom in-clinic fundus photography (refer to Section 11.7) was not completed, as possible, this will be completed at the time of OCT. Fundus photography is an imaging technique used to document changes in the retina and optic nerve.

12. ASSESSMENT OF SAFETY

In addition to assessments of safety, this section includes descriptions of assessments or procedures to characterize the study population (eg, collection of demographic characteristics and medical history).

12.1. Safety Parameters

During the period of time in which COVID-19 contingency measures are in place, remote visits will include AE and concomitant medications review (Section 12.1.2), physical examinations (Section 12.1.3), and clinical laboratory safety assessments (Section 12.1.5). Refer to the Remote Patient Visit Plan for details of safety assessments during remote visits.

12.1.1. Demographics and Medical History

At Visit 1, demographic and medical history information will be collected. This information will be augmented by a detailed collection of subject history in regards to vLINCL6 disease and collection of family history of Batten disease, by or at the Month 3 visit as described in Section 11.3). The demographic information to be collected includes age (from date of birth), sex, race, and ethnicity. As part of the physical examination at Visit 1 (see Section 12.1.3), weight and height will be measured; from these, body mass index will be calculated, and baseline weight, height, and body mass index will be summarized as additional demographic characteristics. Additionally, information on the native language of the subject will be collected.

12.1.2. Concomitant Medications, Non-drug Therapies, and Other Procedures or Accommodations

At each visit, concomitant medications will be reviewed and recorded. For each subject, recorded information is to include any prescription and non-prescription medications, including reason or indication for taking the medication, dosage, frequency, route of administration, and start/stop dates. Changes in regimen or stopping of a concomitant medication, including reason for the change relative to preceding use in this study are also to be recorded.

Also collected will be information on any non-drug therapies, other procedures (eg, physical or occupational therapy, surgeries), or accommodations (eg, wheelchair use). As with concomitant medications, changes in a non-drug therapy or use of accommodations, including the reason for the change relative to preceding use, will be recorded.

12.1.3. Physical Examinations, Including Weight, Height, and Vital Signs

A comprehensive physical examination will be performed at all annual visits and includes recording of weight (Section 12.1.3.1), height (Section 12.1.3.2), and vital signs (Section 12.1.3.3). Comprehensive physical examinations will include assessment of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. Neurological examinations, also performed at each site visit, are described in Section 11.5.

In addition, a chest X-ray will be taken during the screening period. Also, photographs of the subject's infusion site will be taken from Visit 1 (screening/baseline) through Visit 6 of the

study. Prior to administration of AT-GTX-501 on Day 0, multiple potential infusion sites may be photographed.

12.1.3.1. Weight

Weight is to be recorded without shoes.

12.1.3.2. Height

Height is to be recorded without shoes or hats. Height measurements are to be made using stadiometry, when the subject is able to undergo stadiometric measurement.

12.1.3.3. Vital Signs

Vital signs, including systolic and diastolic blood pressures (BPs), respiration rate (RR), pulse rate (PR), and body temperature will be measured at all site visits. Additionally at Visit 2, pulse oximetry, heart rate, and oxygenation are monitored during and after the gene transfer procedure (every 15 minutes ± 5 minutes for 4 hours then every hour ± 15 minutes for 20 hours). Typically, measurements are to be taken with the subject in a sitting or supine position after having rested for 5 minutes. The same position is to be used at all visits. Blood pressure is to be obtained using the same arm for each measurement.

12.1.4. Electrocardiograms

From Day -30 to Day -2 (baseline/screening) and Months 12 and 24, a standard 12-lead electrocardiogram (ECG) will be performed. The overall impression (eg, “normal sinus rhythm”) is to be captured in the ECG eCRF.

Subjects are to rest for approximately 5 minutes before the ECG recording begins and will be in the supine position throughout the ECG evaluation. Parameters expected to be recorded include QT interval, corrected QT interval, QRS interval, PR interval, and heart rate.

The investigator or a suitably qualified delegate will review ECG results and assess any abnormal results as “not clinically significant” or “clinically significant.” Any results that are considered clinically significant may be confirmed in a repeat test at the investigator’s discretion. Clinically significant ECG abnormalities that meet the definition of an AE or SAE are to be recorded in the AE eCRF.

12.1.5. Laboratory Assessments

Additional information on collection, processing, and shipping procedures for any biological samples will be provided in study laboratory manual(s). At the investigator’s discretion, local collection of blood or other samples for completion of safety-related laboratory assessments may be requested at any time.

12.1.5.1. Clinical Safety Laboratory Assessments

Samples collected for clinical safety laboratory assessments, including serum chemistry, hematology, and urinalysis (Table 4) will be performed prior to injection from Day -30 to Day -2 (baseline), Visit 2, and at follow-up visits. During the period of time in which COVID-19 contingency measures are in place, the subject may have samples collected at a local laboratory

for the clinical safety laboratory assessments (see Remote Patient Visit Plan). For subjects who utilize local laboratory sample collection, local laboratory normal ranges are to be reported. Subject's fasting status is to be recorded. For baseline on Day -1 and all post-transfer days except Day 21, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and fibrinogen will be measured. These may also be performed at additional time points at the investigator's discretion. At Visit 1, subjects will also be evaluated to ensure there is no active viral infection (includes HIV or serology positive for hepatitis B or C). Repeat or further blood or urine testing (eg, blood smear and urine microscopy) may be done for abnormal values at the investigator's discretion (reflex testing).

The clinical safety laboratory assessments include ALT, AST, GGT, and bilirubin. These analytes will also be tested as needed, including 1 to 2 weeks before initiating the final dose of steroid (during down-tapering) and 2 weeks after the final dose of steroid (see Section 9.1.1). As needed, these assessments may be performed locally.

Table 4: Clinical Safety Laboratory Parameters

Serum Chemistry	Hematology	Urinalysis
sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate (carbon dioxide), blood urea nitrogen (BUN), creatinine, glucose, bilirubin (total, direct, and indirect), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AlkPhos), gamma-glutamyl transferase (GGT, lactate dehydrogenase (LDH), amylase, troponin, creatine kinase (CK, also known as creatine phosphokinase), albumin, total protein, uric acid	white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, mean platelet volume (MPV), and WBC differential (automated or manual; possibly including neutrophils, segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, and bands [immature neutrophils])	color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, leukocyte esterase, and microscopic urinalysis, including for presence of red blood cells (RBC), white blood cells (WBC), mucus, and epithelial cells

Note: At the time points described in text, these analytes are also measured: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and fibrinogen.

The investigator or a suitably qualified delegate will review laboratory results and assess out-of-range laboratory results as "not clinically significant" or "clinically significant." Results assessed as potentially clinically significant are to be repeated during the same visit whenever possible. If the test result returns after the subject leaves the site, they will be immediately contacted. For local residents, they will be asked to return to the outpatient clinic for a repeat test. For non-local residents, arrangements will be made to have the test repeated by a clinic/laboratory close to home or by their primary care physician. To avoid any confusion for the primary care physician, they will have been informed (refer to Section 12.6.1) of the subject's participation in the study. If the laboratory finding constitutes as an AE that requires treatment, this may be carried out by the subject's primary care physician or another doctor. Any obtained copies of repeat laboratory tests or other relevant medical records will be added to the

subject's research chart. The investigator is to consider repeat testing of persistent clinically significant results until the analyte returns to normal levels or until an etiology is determined.

Clinically significant laboratory abnormalities are to be captured as an AE or SAE, as appropriate.

The investigator or a suitably qualified delegate will sign and date all laboratory reports.

12.1.5.2. Confirmatory Genotyping

Confirmatory genotyping will be done if the subject does not have a genotype report in their source file from a CAP/CLIA-certified laboratory (or a non-US laboratory with an equivalent national accreditation/certification). As needed, a blood sample for this confirmatory genotyping will be collected at Visit 1.

12.1.5.3. Immunogenicity Assessments

Blood sample collection for immunogenicity assessments will be performed at baseline and at each site visit from Day 7 through Month 24.

Assessments will include measurements of anti-AAV9 and anti-CLN6 antibodies and measurement of T-cell responses (eg, separate IFN-γ ELISpot assays to detect T-cell responses to CLN6 peptides or AAV9) will occur from Day -30 to Day -2 (baseline/screening), at follow-up site visits on Days 7, 14, 21, and 30 (Visits 3 to 6), and at Months 6, 9, 12, 18, and 24, (Visits 7 to 10, Visit 12, and Visit 14). If there is insufficient sample volume to complete an assessment, missing immunogenicity assessments will not be considered a protocol deviation.

12.1.5.4. Viral Shedding

The extent of viral shedding is not fully understood. Assessment of viral shedding will be performed in all subjects as part of this gene transfer protocol. If the subject has a sibling who is affected (or potentially affected) and may potentially be treated with gene transfer, the subject's parents will be advised to keep siblings separated during the time of potential viral shedding and appropriate measures will be taught to try to prevent exposure.

Once at baseline (Visit 1) then at each follow-up site visit, starting with Visit 3, saliva, stool, and urine will be collected for assessment of viral shedding. Collection of urine, saliva, and stool for assessment of viral shedding may not continue throughout the study; this will be determined individually for each subject and for each sample type. For an individual subject, once a sample type (ie, urine, saliva, or stool) has 3 consecutive negative results, that sample type will no longer be collected for assessment of viral shedding.

The specimens will be tested with a quantitative polymerase chain reaction (qPCR) method to measure the presence of AAV vector genomes in real time (at least for those subjects with a known or potentially affected sibling); for subjects without siblings, the qPCR testing is to be completed before the subject's next visit. Samples awaiting testing or remaining samples following completion of qPCR testing will be placed in a deoxyribonuclease/ribonuclease-free Eppendorf tube with locking top. The tubes will be stored in a -80°C freezer.

12.1.5.5. Samples for Reanalysis or Future Assessments

Any biological specimens remaining at the end of the study may be used for re-assay, future assay development and validation, or for future exploratory analyses to improve the understanding of vLINCL6 disease and its management.

Additionally, for subjects who consent, additional biological sample collection for safety, efficacy, or other research assessments may also be performed at each annual visit. Biological samples collected may include blood, saliva, stool, urine, and/or CSF.

Lumbar puncture will be performed on Day 0 for administration of AT-GTX-501 and collection of CSF. Any additional CSF collection at Month 24 will be as per the consent documents/text related to anesthesia, as anesthesia is required for the lumbar puncture. The potential additional CSF collection at Month 24 would occur following any other EUAs (described in Section 11.9).

12.2. Adverse and Serious Adverse Events

The investigator and study personnel are responsible for detecting, documenting, and reporting AEs and SAEs. For each subject, reporting of AEs and SAEs is to begin after written informed consent is provided. Through the Month 24 visit, all AEs will be followed until resolution or stabilization. Any AEs ongoing at the conclusion of the study that are not considered related to AT-GTX-501 will not be followed after the subject completes the Month 24 visit.

Throughout the study, opportunities to report AEs will be provided. The definitions of AE and SAE are in Section 12.2.1.1 and Section 12.2.1.2, respectively. Reporting instructions for AEs and SAEs are in Section 12.5.1 and Section 12.5.2, respectively.

If needed to determine appropriate treatment or the causality of AEs/SAEs, appropriate follow-up procedures will be conducted.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product, biologic, or medical device (medicinal products). The AE does not necessarily have a causal relationship with the medicinal product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

Therefore, AEs may include:

- New signs, symptoms, conditions, or illnesses
- Exacerbation (eg, increase in intensity, frequency) of pre-existing signs, symptoms, conditions, or illnesses after subjects provide informed consent
- AEs related to a protocol-required procedure
- Abnormal laboratory findings deemed clinically significant by the investigator

- Physical or neurological examination changes deemed clinically significant by the investigator
- Other abnormal medical findings (eg, ECG) that were not documented at Visit 1 and/or, in the investigator's opinion, represent a clinically significant change in the subject's health during study participation
  - Medical findings at Visit 1 (eg, ECG) that were not previously provided as medical history but can be determined as starting prior to Visit 1 are not considered AEs and are to be recorded as medical history

12.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (eg, baseline, treatment, or follow-up) that fulfils any of the following:

- Results in death
- It is life-threatening (places the subject at immediate risk of death)
  - As assessed by either the investigator or Amicus
  - This does not include an AE that, had it occurred in a more serious form, hypothetically might have caused death.
- It requires inpatient hospitalization or prolongs existing hospitalization
  - Emergency room/department or outpatient treatments that do not result in admission do not have to be reported as an SAE, unless another SAE criterion is met.
    - Events assessed and treated in these circumstances are to be captured as AEs.
  - Hospitalizations for elective or pre-planned treatment of a pre-existing condition do not have to be reported as SAEs provided the condition is documented in the subject's source documents and has not worsened since written informed consent was first completed
  - Hospitalization signifies the subject has been admitted, regardless of duration, for observation and/or treatment that would not have been appropriate in a physician's office or outpatient setting.
  - Hospitalizations solely based on logistics (eg, subject is admitted due to limited hospital accessibility for what would otherwise be an outpatient procedure) do not have to be reported as SAEs, provided they are clearly defined as such in the subject's source record.
- It results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- It results in a congenital anomaly/birth defect

An important medical event that may not result in any of the above serious outcomes may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the

subject and may require medical or surgical intervention to prevent any of the above serious outcomes. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

If the following 4 elements are known regarding an SAE, the event must be reported as described in Section 12.5.2:

- Identifiable subject
- AE term
- Study treatment, AT-GTX-501
- Identifiable reporter

Additionally, the investigator's assessment of an event's relationship to AT-GTX-501 (see Section 12.3) is essential for Amicus to appropriately process the report and is to be included.

Subjects are to be informed that they are to report events meeting the definition of seriousness to study personnel as soon as possible (and to not wait until their next study visit). If a non-serious AE becomes an SAE, the change in status is to be appropriately entered in the case report form (CRF) and the subject's source record, and reported to Amicus as described in Section 12.5.2.

12.2.1.3. Expected Events Related to Disease Progression

Subjects enrolled in this clinical protocol are expected to present clinically with events related to natural progression of the disease.

Any AEs determined to be due to the underlying disease progression may not be subject to the expedited reporting requirements outlined in Section 12.5.3. Changes in these disease symptoms are to be reviewed by the investigator or a medically qualified sub-investigator. Expected or anticipated changes in these clinical conditions may not qualify as AEs. However, if there is a clinically relevant worsening of a sign or symptom of the disease under treatment and the outcome fulfills the definition of an AE, it is to be reported.

Anticipated vLINCL6 disease-related signs and symptoms related to progression of the disease are:

- Impaired motor function
- Impaired speech
- Impaired cognitive function
- Movement disorder
- Seizures
- Hallucinations
- Sleep abnormalities
- Behavioral difficulties
- Blindness
- Irritability
- Dementia

12.2.1.4. Anticipated Adverse Events of Laboratory Findings Related to Intervention

Following gene transfer, elevation of transaminases (levels up to 5X the upper limit of normal [ULN]) with preserved liver synthetic function and no significant elevation in GGT are anticipated and will be recorded as AEs and graded per CTCAE guidelines. Mild decreases in leukocyte and lymphocyte counts within the first 30 days after gene transfer have been observed in other studies of AAV-mediated gene transfer. Such transient decreases in lymphocytes or leukocytes will be recorded as AEs but considered anticipated.

Leukocytosis and neutrophilia during prednisone or prednisolone treatment:

> An elevation of up to 5000 cells/mm^3 above the subject's baseline value is expected in the neutrophil count (the primary granulocyte in circulation) and, consequently, in the leukocyte count within 5 hours of initiating prednisone or prednisolone therapy, based upon studies in healthy adult volunteers. This occurs secondary to release of granulocytes from the marginated pool into the circulation accompanied by an increase in the size of the marginated granulocyte pool due to steroids (Munroe, Mitchison et al. 1997; Cotman, Vrbanac et al. 2002). This steroid effect may be seen with increased steroid dosing.

12.2.1.5. Dose-limiting Toxicity

A DLT is defined as any unanticipated AE that is related to AT-GTX-501 (events assessed by the investigator as definitely, probably, or possibly related) and is Grade 3 or higher, according to the CTCAE version 4.0 (published 28 May 2009). See Section 12.4.1 for further description of the CTCAE grades.

12.3. Relationship to Study Treatment

The investigator or a medically qualified sub-investigator will review each AE and assess its relationship to AT-GTX-501 based on available information and according to the following guidelines:

- **Definite (1)**: A reaction that follows a distinct temporal relationship from administration of the study treatment that follows a known reaction to the agent or chemical group of the study treatment; and that cannot be explained by the subject's clinical state or other factors
- **Probable (2)**: A reaction that follows a reasonable temporal sequence from administration of the study treatment; that follows a known or expected response pattern to the suspected study treatment; and that could not be reasonably explained by the known characteristics of that subject's clinical state
- **Possible (3)**: A reaction that follows a reasonable temporal sequence from administration of the study treatment; that follows a known or expected response pattern to the suspected study treatment; but that could readily have been produced by a number of other factors
- **Unlikely (4)**: A reaction that does not follow a reasonable temporal sequence from administration of study treatment. However, causality from the medication cannot be excluded

- **Unrelated (5)**: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study treatment

For the purpose of the definition of DLTs (as defined in Section 12.2.1.5) and expedited SAE regulatory reporting obligations (ie, to regulatory authorities and the Institutional Review Board [IRB]), events assessed by the investigator as definitely, probably, or possibly related to AT-GTX-501 will be considered "related" to AT-GTX-501. Events assessed as unlikely or unrelated will be considered "not related" to AT-GTX-501.

12.4. Recording Adverse Events

For each subject, reporting of AEs begins after written informed consent is completed. Adverse events may be volunteered spontaneously by the subject or discovered as a result of general, non-leading questioning by or observation by study personnel.

Adverse events will be recorded in the CRF and subject's source record beginning from the time written informed consent is completed through the end of this study. The AE term is to be reported in standard medical terminology when possible. A single diagnosis is to be entered when known. If a clear diagnosis cannot be determined at the time of CRF and the subject's source record entry, each sign and symptom is to be recorded individually until a final diagnosis is established.

For each AE, the following is to be recorded:

- Date and, as possible, time the AE started and ended
- Action(s) taken with study treatment
- Outcome (resolved, resolved with sequelae, ongoing, or fatal)
- Intensity (see Section 12.4.1)
- Relationship to AT-GTX-501 (see Section 12.3)

Additional required information may be detailed in CRF completion guidelines.

All conditions (including those that are considered related to vLINCL6 disease), signs, or symptoms that are reported as part of the subject's medical history are only to be reported as AEs if they worsen (ie, increase in intensity) following the completion of Visit 1. If a nonserious AE becomes serious, the SAE must be reported as described in Section 12.5.2.

12.4.1. Assessment of Adverse Event Intensity

When the determination of AE intensity rests on medical judgment, the determination of intensity must be made with the appropriate involvement of the investigator or a qualified sub-investigator.

The definitions/classification for rating intensity will follow the guidelines outlined in CTCAE version 4.0 (published 28 May 2009), which includes:

- **Grade 1 Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- **Grade 2** **Moderate**; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- **Grade 3** **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- **Grade 4** **Life-threatening consequences**; urgent intervention indicated
- **Grade 5** **Death** related to AE

Note: A semi-colon indicates 'or' within the description of the grade.

Note: Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Note: Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.4.2. Distinction Between Serious and Severe Adverse Events

It is important to distinguish between SAEs and AEs that are severe (Grade 3 or greater). Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may not be considered serious. Adverse events of severe intensity are not SAEs unless any of the listed outcomes in Section 12.2.1.2 occurs. Adverse events of any intensity must be reported as SAEs if at least any of the listed outcomes in Section 12.2.1.2 occurs.

12.4.3. Changes in Laboratory Values, Blood Pressure, or Other Measures

Consistent with Section 12.2.1.1, out-of-normal range results for laboratory values, blood pressure, and other measures (eg, pulse) are not required to be reported as AEs. Only results that the investigator deems clinically significant are to be reported as an AE or SAE.

12.5. Reporting Adverse Events

The COVID-19 contingency measures (see Remote Patient Visit Plan) do not affect the reporting timelines for AEs and SAEs described below in Section 12.5.1, Section 12.5.2, and Section 12.5.3.

12.5.1. Reporting of Adverse Events

The clinical course of each AE is to be followed according to accepted standards of medical practice.

In the case of withdrawal due to an AE or SAE, the subject is to be followed until resolution of the event, or until (in the opinion of the investigator) the AE has stabilized and the investigator does not expect any further improvement or worsening of the subject's condition and/or the subject has been referred to their primary physician for appropriate management of the ongoing event. Relevant clinical assessments and laboratory tests are to be repeated as clinically appropriate, such as until final resolution or stabilization of the event(s). Reasonable efforts are

to be made to contact any subject who fails to attend any follow-up appointments in order to ensure that he/she is in satisfactory health.

If the investigator considers it necessary to report an AE in a study subject more than 30 days after their last visit, he or she is instructed to contact Amicus to determine how the AE must be documented and reported.

Investigators are also responsible for reporting AE information to the relevant IRB in accordance with the requirements of their institutions.

12.5.2. Reporting of Serious Adverse Events

All SAEs are to be documented and reported to Amicus immediately, but no later than **24 hours of any study personnel knowledge of events**, regardless of any assessment of the event as related or not related to study treatment. Each SAE report is to be faxed to the designated safety fax number (+ 1 866-422-1278) to ensure appropriate dissemination and processing of the information. An alternate email address is provided as a backup (Table 1), if the fax transmission is unsuccessful.

If multiple SAEs are identified in a subject simultaneously, separate SAE reports are to be completed for each event.

The SAE forms, which will be provided by Amicus, are to be as complete as possible, with all known information at the time included. Reporting timelines (as described above) are not to be delayed while obtaining or preparing supporting information. All known details of the SAE, including an assessment of the causal relationship between the event and AT-GTX-501, are to be included in the initial report. All available relevant supporting documentation (eg, admission and progress notes, results of diagnostic evaluations/procedures/examinations, etc) available at the time of initial reporting are also to be included. All supporting documents are to be thoroughly reviewed and de-identified in accordance with local data privacy regulations prior to sending to Amicus. If submitted by fax, the subject's study number must be included on each page included in the fax. If submitted by email, the subject's study number must be included in the subject line of the email.

Information not available at the time of the initial report (eg, event end date and outcome, discharge summary, etc) must be faxed to the designated safety fax number **within 24 hours of any study personnel knowledge of the information** (or emailed if the fax is unsuccessful). As when included in initial reports, all supporting documents are to be thoroughly reviewed and de-identified in accordance with local data privacy regulations prior to submission to Amicus. If submitted by fax, the subject's study number must be included on each page included in the fax. If submitted by email, the subject's study number must be included in the subject line of the email.

For any AE resulting in death, any available autopsy/pathologist's report is to be supplied.

Concomitant medications, AE, or other information obtained through SAE reporting must also be recorded in the appropriate CRF. If new medical or medication history is obtained via SAE reporting, the addition of the data to the clinical database is to be reported in an appropriate CRF.

If the investigator becomes aware of an SAE in a subject or receives an unsolicited report of an SAE from a subject more than 30 days after their last study visit and considers the event

possibly, probably, or definitely related to previously receiving AT-GTX-501, they are instructed to contact Amicus to determine how the SAE is to be documented and reported.

12.5.3. Additional Reporting Requirements for Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, unexpected, and associated with the use of study treatment has additional reporting requirements. For each SAE, Amicus will determine the expectedness of AEs according to current safety reference document.

Amicus is responsible for processing suspected unexpected serious adverse reactions (SUSARs). These SUSAR reports are also referred to as alert reports, expedited safety reports, and investigational new drug (IND) safety reports. A SUSAR is defined as any SAE that is determined to be associated with the use of the study treatment and is unexpected (not currently listed in the current safety reference document, as described in Section 12.2.1.3, or is not listed at the specificity or severity that has been observed).

Amicus will ensure SUSARs are reported to the FDA, in accordance with local laws.

- If the SUSAR is fatal or life-threatening, regulatory authorities and ethics committees are to be notified within 7 calendar days after Amicus learns of the event.
- If the SUSAR is not fatal or life-threatening, regulatory authorities and ethics committees are to be notified within 15 calendar days after Amicus learns of the event.

Additionally, safety updates will be provided periodically to the FDA and the relevant IRB. These updates will include information on SUSARs as well as other relevant safety findings.

12.6. Other Reporting Situations

12.6.1. Reporting Information from Subject's Primary Care Physician

Throughout the study, any routine or non-routine visits to a subject's primary care physician, or other medical care received during the study, are to be reported to study personnel. Informed consent will include consent to collect any relevant medical records from the subject's other medical care providers. Also, close communication will be established by the investigator or their delegate with the primary care physician for each subject and will be maintained throughout the study. For the primary care physician, the important hallmarks of the study along with the proposed reporting plan will be explained. Laboratory reports, hospitalizations, clinical notes, and any other relevant medical records will be requested at the time of their occurrence.

As appropriate, the investigator or their delegate will report salient information received on the appropriate CRF (eg, AEs and concomitant medications).

13. STATISTICS

An overview of known statistical considerations is included below. Descriptions of all endpoints and their planned analyses will be detailed in the Statistical Analysis Plan (SAP).

13.1. Endpoints

13.1.1. Safety Endpoints

The safety endpoints will be defined based on parameters from the assessments described within Section 12.

13.1.2. Efficacy Endpoints

The efficacy endpoints will be defined based on parameters from the assessments described within Section 11. The primary efficacy outcome will be based on the Hamburg Motor and Language scores.

13.2. Statistical Methods

13.2.1. General Considerations

As appropriate, data analyses will be analyzed both with respect to the subject's age and respective date of receipt of AT-GTX-501. If a subject has 1 or more siblings who was untreated and for whom relevant data are available, or a sibling who was also treated with AT-GTX-501, relevant comparisons will be presented. If needed, separate analyses will be performed for subjects who receive other treatments that may be disease-altering (eg, another approach to gene transfer or other investigative or prescription product). Natural history data on patients with vLINCL6 disease and/or pre-treatment data from subjects in Study AT-GTX-501-01 may also be included in analyses. As needed and as possible, analyses will account for changes in assessment methodology, such as a change in the cognitive assessment as per the study neuropsychologist (see Section 11.6).

By-subject listings will be prepared for all eCRF-collected data.

13.2.1.1. Baseline Definition

Baseline is generally defined as the measure immediately preceding receipt of AT-GTX-501.

13.2.1.2. Descriptive Statistics

Data will be summarized with descriptive statistics and/or response frequencies. For continuous data, descriptive statistics will include sample size (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum. For categorical data, descriptive statistics will be category frequency counts and proportions (or percentages) of the number of subjects used in the analysis. The counts for the categories of 'Missing', 'Unknown' or 'Not applicable' will be provided as appropriate, but the percentages will not be provided.

13.2.1.3. Handling of Missing Data

Handling of missing data will be as described in the SAP.

13.2.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized as described in the SAP.

13.2.3. Exposure

Descriptive statistics for duration since administration of AT-GTX-501 will be provided.

13.2.4. Safety Analyses

All safety analyses will be performed using the safety population. In addition to the summaries described in the below subsections, a brief tabular narrative for each subject describing age, sex, race, ethnicity, and other relevant demographic characteristics may be prepared. The tabular narrative may also include such things as each subject's genotype, study status (ie, duration since treatment, completed the study [Yes/No], and [if "No"] reason for discontinuing the study prematurely), relevant AE information, and medical and medication history.

13.2.4.1. Adverse Events

Adverse events will be coded to System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; version 20.1 or later).

All AEs that occur during this study after receipt of AT-GTX-501 will be classified as TEAEs. Summaries of AEs and TEAEs will be prepared overall and for each subject. Summaries of non-serious AEs and TEAEs (ie, all except SAEs) will also be prepared to support future ClinicalTrials.gov reporting requirements.

13.2.4.1.1. Summaries of Adverse Event Incidence Rates for All Subjects

The number and percentage of subjects with TEAEs will be summarized by preferred term and then also by SOC and preferred term within each SOC. Additional displays will present TEAEs by intensity (5 CTCAE levels), by relationship to study treatment (Related Events: definite, probable, and possible; Unrelated Events: unlikely and unrelated), and by outcome of events.

Moreover, the number of TEAEs (as opposed to the number and percentage of subjects) will be presented. A summary of non-serious TEAEs (all TEAEs except SAEs) will also be presented by SOC and preferred term.

13.2.4.1.2. Summaries of Adverse Event Incidence Rates for Serious Adverse Events, Adverse Event Dropouts, and Death

Summaries of SAEs will be prepared overall and for each subject.

The number and percentage of subjects who experienced SAEs and/or TEAEs leading to withdrawal from the study will be presented by SOC and by preferred term within each SOC. Serious TEAEs and TEAEs leading to withdrawal from the study will be similarly presented by intensity (5 CTCAE levels), by relationship to AT-GTX-501 (Related Events: definite, probable, and possible; Unrelated Events: unlikely and unrelated), and by outcome of events. Moreover, the number of treatment-emergent SAEs (as opposed to the number and percentage of subjects) and TEAEs leading to withdrawal will be presented.

Listings of SAEs, TEAEs leading to withdrawal from the study, and deaths, if any, will also be provided.

13.2.4.2. Clinical Safety Laboratory Data

Routine clinical safety laboratory data will include serum chemistry, hematology, and urinalysis. Quantitative laboratory test result summaries will include N, mean, standard deviation (SD), median, and range. Qualitative tests (eg, certain urinalysis assessments) will be summarized by the number and percentage of subjects in each category, as appropriate.

Descriptive statistics for laboratory data at each visit starting from baseline and change from baseline to each post-baseline visit will be presented. Data will be attributed to scheduled visits as described in the SAP.

Potentially clinically significant (PCS) laboratory values at any time during the study may be summarized by laboratory parameter. The PCS criteria for laboratory values would be as defined in the SAP.

13.2.4.3. Vital Signs

Descriptive statistics for vital signs at each visit starting at baseline to each post-baseline visit will be presented for systolic and diastolic BPs, body temperature, HR, and RR. Change from baseline to each post-baseline visit may also be presented.

The PCS vital sign changes at any time during the study may be summarized by parameter. The PCS criteria for vital signs would be as defined in the SAP.

13.2.4.4. Physical Examinations

Baseline physical examination results will be summarized by body system, presenting the number and percentage of subjects judged to be normal, abnormal, or not performed for each body system.

For subjects with a physical examination during the study, a shift table of changes from baseline will be presented by body system for each post-baseline visit.

13.2.4.5. Electrocardiograms

Descriptive statistics for quantitative ECG data at each visit starting from baseline and change from baseline to each post-baseline visit will be presented.

The PCS values for quantitative ECG data at any time during the study may be summarized by parameter. The PCS criteria for quantitative ECG data would be as defined in the SAP.

13.2.4.6. Concomitant Medications and Non-drug Therapies

The number and percentage of subjects using concomitant medications will be summarized by their anatomical therapeutic chemical (ATC) class and preferred term within each ATC class. Concomitant medications will be coded into their ATC class and preferred term using the World Health Organization Drug Dictionary Enhanced (WHO DDE; Sep 2014 or later version).

Non-drug therapies, other procedures (eg, physical or occupational therapy, surgeries), or accommodations (eg, wheelchair use) will be listed.

13.2.4.7. Subgroup Analyses

Subgroup analyses may include presentation by age group and sex for TEAEs, SAEs, and any TEAEs resulting in withdrawal.

13.2.5. Efficacy Analyses

Analyses of all efficacy endpoints will be as described in the SAP. In general, descriptive statistics for efficacy data at each visit starting from baseline and change from baseline to each post-baseline visit will be presented.

For the primary efficacy endpoints, analyses comparing study data with natural history data will be performed as described in the SAP.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP guidelines. The procedures outlined in the protocol and CRFs will be carefully reviewed by the investigator and study personnel prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care, and wellbeing of subjects.

Amendments will be submitted to the IRB for their review and approval prior to implementation. When an amendment to the protocol substantially alters the study design or increases potential risk to the study subject, the informed consent form (ICF) will be revised and, if applicable, consent to continue the subject's participation will again be obtained.

14.2. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB, or an auditor authorized by Amicus may request access to all source documents, eCRFs, and other study-related documentation for a site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who is to provide support at all times for these activities. Source documents (including medical records) and other study documents may be copied during an audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

The investigator is to contact Amicus immediately if contacted by a regulatory authority regarding an inspection or audit.

14.3. Institutional Review Board

The investigator for each site must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the ICF, assent form (if/when applicable), and recruitment materials, must be maintained by the investigator and made available for inspection.

14.4. Data Safety Monitoring Board

A DSMB is in place to regularly monitor the safety of subjects. The membership and procedures are specified by a DSMB Charter.

14.4.1. Data Safety Monitoring Board Responsibilities

The responsibilities of the DSMB include:

- Approving the DSMB Charter, which outlines the responsibilities, functions, rules for conduct, and the basis for monitoring the trial
- Reviewing reports relevant to trial conduct and assumptions, safety variables, making recommendations regarding changes or adjustments and preserving the trial integrity

- Suggesting modifications of outputs for the next DSMB meeting (if necessary and applicable)
- Suggesting modifications to the trial protocol; modifications may include, but are not limited to: changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in trial procedures or trial conduct, if applicable (the DSMB should recognize that making suggested modifications after having seen study data has the potential to jeopardize the integrity of the trial; therefore, such recommendations should generally be made only to protect the safety of the participants in the trial)
- Recommending either continuation of the trial according to the protocol and any relevant amendments or discontinuation of the trial (with provisions for orderly discontinuation in accordance with GCP)

14.4.2. Data Safety Monitoring Board Reporting and Meetings

Reports describing the status of the study will be prepared and sent at the DSMB's request. The DSMB met prior to dosing of the first subject and was provided with a report after dosing Subject 1. A teleconference with the DSMB was conducted after dosing of Subject 3.

Routine meetings of the DSMB will be held as per their charter, via video conference or webinar call. All DSMB discussions are confidential. An ad hoc meeting of the DSMB may be called at any time by the Chairperson should ethical or patient safety issues arise.

Reports will include, but are not limited to, the following:

- A brief narrative of the study status, including the target enrollment, current and projected time to completing enrollment, and a brief description of any significant events and/or difficulties
- A brief narrative for each subject describing gender, age, race and ethnicity and other relevant demographic characteristics, as well as a brief description of his/her study status (ie, dose level, visit number, AE information)
- A timeline outlining the study progress relative to visit number for each subject, as well as time points for each SAE/DLTs, and a total of AEs for each participant
- A summary of clinically significant laboratory test results
- A listing of protocol deviations

14.4.3. Data Safety Monitoring Board Membership

Each DSMB member will be an expert in clinical trials conduct, one or more fields relevant to the disease under study, the evaluation of safety to be monitored during the trials, and/or the biostatistical evaluation of the study results. The members are to have experience in performing clinical trials and have knowledge of GCP guidelines and a general understanding of regulatory requirements for drug development. Statistical support for this DSMB is provided by an experienced independent biostatistician from Amicus.

The DSMB membership will consist of individuals completely independent of the investigator. Some DSMB members, due to their expertise, may be from an institution where the study is

being conducted. In this event, the situation will be made known to the DSMB membership. Moreover, the DSMB member will not discuss or become involved in any discussions or communications with the investigator that concern any matters or responsibilities of the DSMB.

Each DSMB member is to notify Amicus in writing of any actual or potential conflict of interest between their personal interests and the role of the DSMB. Conflicts of interest can include professional, proprietary, and miscellaneous interests. DSMB members are under a continuing obligation to notify Amicus promptly, in writing, through the DSMB chairperson, of any further potential conflicts of interest arising during the time they are serving on the DSMB.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Amicus may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit, or inspection, the investigator (and medical institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified during the regulatory audit or inspection.

16. ETHICS

All investigators are required to certify their compliance with ICH E6 GCP and, as applicable, their respective country's applicable laws and regulations.

Amicus will ensure that the conduct, monitoring, auditing, recording, analysis, and reporting of clinical study results are in accordance with ICH GCP, providing assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of subjects are protected.

16.1. Ethics Review

Prior to initiation of a study site, Amicus will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH GCP and applicable country-specific regulatory requirements.

The final study protocol, including the final version of the ICFs (and assent forms, when applicable), must be approved or given a favorable opinion in writing by the IRB. The investigator must submit written approval to Amicus or their designee before he or she can recruit any subject into the study. Investigators may enroll subjects from their existing or incoming patients, ask other physicians for referrals of suitable patients, or advertise the study in public media after both review and approval by Amicus and the IRB.

The investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, if applicable, as local regulations require.

16.2. Ongoing Information for Independent Ethics Committees

The information listed below will be submitted to the relevant independent ethics committee (ie, the IRB) according to timelines specified by the documented submission policies and procedures, or by local laws:

- Information on AEs and SAEs
- Expedited safety reports
- Periodic reports on the progress of the study

Submissions may be made by Amicus (or designee) or by the investigator. The parties responsible for submissions are to be identified and documented prior to the enrollment of a subject to this study.

16.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH, GCP, and applicable regulatory requirements.

16.3.1. Study Protocol, Amendments, and Deviations

If a clarification on a procedure or an error is found in the protocol, a protocol clarification memo will be sent to the study site and the IRB before an amendment is issued.

Changes to the administrative aspects of the study (eg, changes in contact information or study personnel) will not require formal protocol amendments or IRB approval, but can be treated as administrative amendments. However, the IRB is to be kept informed of such changes.

Non-administrative changes to the protocol, initiated either by Amicus or the investigator, will require a formal amendment procedure. Approval of all amendments must be obtained from Amicus, the IRB, and regulatory authorities (in accordance with local requirements) prior to implementation.

The procedures outlined in the protocol and case report forms will be carefully reviewed by the investigator and study personnel prior to study initiation and following protocol amendments to ensure appropriate interpretation and implementation. Protocol deviations that may significantly impact subject safety or scientific integrity (eg, changes to eligibility criteria, addition or deletion of tests, dosing, duration of treatment, and/or other aspects of study design) are not permitted under GCP or by Amicus, unless necessary to eliminate an immediate hazard to the subject(s).

Where Amicus and/or the investigator must take urgent safety measures to protect subjects from an immediate hazard or provide proper care, a protocol deviation may be allowed prior to obtaining approval from the IRB (and/or regulatory authorities) according to 21 CFR 312.30(b) (2). In such cases, Amicus and the IRB must be notified within 1 business day.

Amicus and the IRB, where required by local laws, must be informed of all protocol deviations and violations, and the investigator shall document such protocol deviations and violations in subject source documents and eCRFs.

No amendments to the protocol will be implemented prior to agreement from Amicus and prior to approval from appropriate authorities.

16.3.2. Delegation of Investigator Duties

The investigator is to ensure that all persons assisting with the study are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatment, and their study-related duties and functions.

As appropriate, Amicus will select a coordinating investigator as a representative of all investigators for this study. Each investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom they delegate significant study-related duties.

Even if the investigator delegates any study-related duties to other qualified members of his or her study personnel, the investigator retains ultimate responsibility for obtaining written informed consent for study subjects; for ensuring that the investigation is conducted according to the protocol, the signed investigator statement (Form FDA 1572), and applicable regulations; for protecting the rights, safety, and welfare of study subjects; and for the control of the study treatment under evaluation.

16.4. Written Informed Consent

Written informed consent is to be obtained for each subject before any study-related procedures are performed and after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In addition to the subject's preceding informed consent for the study, an additional informed consent is to be obtained using the NCH "Informed Consent to Participate in Telehealth Services" prior to any remote subject visits being performed.

As the subjects in this study are under the legal age of consent, the ICF is to be signed by the personally dated signature (thumbprint or mark) of the subject's parent, guardian, or legally-authorized representative in accordance with the relevant country and local regulatory requirements. Where allowed, subjects under the legal age of consent may sign an assent form. Any pediatric subject assent would be collected once the investigator judges that to be appropriate, based on the cognitive abilities of the subject. The ICF and, when applicable, the assent form, are to be in a language understandable to the individual providing consent and is to specify who informed the individual providing consent. Where required by local laws, the person who informs the individual providing consent must be a physician.

The individual providing consent is to be provided the opportunity to read the informed consent document and have all their questions and concerns addressed before giving consent in writing. If the individual is unable to read, an oral presentation and explanation of the ICF and information must take place in the presence of an impartial witness. Details about why an oral presentation was used, how the information was presented, and how the individual providing consent provided consent are to be described in the subject's source documents.

A copy of the signed informed consent will be provided to the individual providing consent and the original will be retained in the Investigator Site File. An entry is to be made in the subject's dated source documents and eCRF to confirm that informed consent was obtained prior to any study-related procedures and that the individual providing consent received a copy of the signed informed consent.

The witness and the person conducting the informed consent discussions must also sign and personally date the consent document. Until a signed written informed consent has been obtained, the investigator will not undertake any measures specifically required for this study.

The investigator will inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The principles of informed consent in the Declaration of Helsinki, in ICH GCP, and in US 21 CFR Part 50 (Protection of Human Subjects) will be implemented before any protocol-specified procedures or interventions are carried out.

The individual providing consent will be informed that the subject may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

When necessary, the ICF will be revised and the informed consent procedure will be repeated for each affected subject.

16.5. Confidentiality

Subject names will not be supplied to Amicus. A unique subject number will be recorded in the eCRF, and if the subject name appears on any other document (eg, a laboratory report), it must be obliterated on the copy of the document to be supplied to Amicus. Study findings stored on a computer will be stored in accordance with local data protection laws. The subject will be informed that representatives of Amicus, the IRB, or regulatory authorities may inspect their source documents to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator must assure that the subjects' anonymity will be maintained through a personal subject identification list (subject numbers with corresponding subject names). On all study documentation, with the exception of the consent/assent form and subject identity logs, subjects are only to be identified by their unique identification code and initials and are not to be referred to by name.

16.6. Reporting and Posting Requirements

Amicus will be responsible for registering this study in a public registry that meets the requirements specified by the International Council of Medical Journal Editors, such as ClinicalTrials.gov and EudraCT for posting of study results. Investigators will provide contact information to Amicus for the study listing.

16.7. Legal and Financial Aspects

16.7.1. Liability and Insurance

Liability and insurance provisions for this study are provided in separate agreements.

16.7.2. Financial Disclosure

Before the start of the study, the investigator will disclose to Amicus any proprietary or financial interests he or she might hold in the AT-GTX-501 or Amicus, as outlined in the financial disclosure form provided by Amicus.

The investigator agrees to update this information in case of significant changes during the study or within 1 year of its completion. The investigator also agrees that, where required by local laws or regulations, Amicus may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Where required by regulation, the investigator will disclose their financial interests to the subjects in the ICF (and assent forms, when applicable). Also, the investigator or Amicus, on behalf of the investigator, will submit the financial arrangements for the study to the regulatory authorities or to the IRB.

Any sub-investigator to whom the investigator delegates significant study-related responsibilities will also provide financial disclosures.

17. DATA HANDLING AND RECORDKEEPING

17.1. Data Management

All data and observations will be documented on CRFs by transfer of information from source documentation. A study monitor will have access to the data to monitor adherence to the protocol and to applicable FDA regulations, and maintenance of adequate and accurate clinical records. A CRF will be completed for every subject registered for participation in the study. Each CRF is to be completed as information becomes available or within 3 business days of a study visit.

The study CRFs will be reviewed in detail by the study monitor on a regular basis, for which purpose the study monitor will have access to subjects' medical records, laboratory data, and other source documentation. If errors or omissions are found in the course of a data audit, or if clarification of data is required, the CRF(s) in question will be corrected by the investigator. Data resolution activities may be generated for omissions or clarifications, to be completed, signed, dated, and maintained as a part of the CRF.

A web-based database was created and is managed by authorized users. Paper CRFs are transcribed to this web-based database. Data is extracted from source documents (laboratory reports, EEG reports, etc) and transferred to the database as well. All source documents will be kept in the subject's research chart. The secured portal features view and edit capability with field validations for quality controls, change history attribute, and reporting.

After completion of the study by an individual subject, the investigator will sign and accept each indicated CRF. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the CRF.

An external contract research organization (CRO) may also monitor the study in a regular basis to make sure the study is conducted in compliance with all regulatory aspects of the protocol.

17.2. Inspection of Records

Amicus or their designees, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow these monitors to inspect the drug storage area, drug stocks of AT-GTX-501, drug accountability records, subject medical records and study source documents, and other records relative to study conduct.

During the COVID-19 pandemic, remote monitoring will be implemented. The clinical site will remove subject identifiers in the source documents and upload to a secure Sharepoint site. The clinical research organization (CRO) will use these source documents as a tool to perform remote source document verification of study assessments.

17.3. Retention of Records

The investigator must obtain approval in writing from Amicus before destruction of any study-related records.

Essential documents are to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of

clinical development of AT-GTX-501. However, because of international regulatory requirements or country-specific requirements, Amicus may request retention for a longer period. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Amicus' standard operating procedures, and/or institutional requirements.

Prior to any decision regarding the disposal or destruction of study documents, the investigator or CRO is to contact Amicus, who may request that the site take alternative actions other than disposal or destruction of study documents.

Essential documents include the following:

- Signed informed consent documents for all subjects, including all ICFs completed following any protocol amendment. When applicable, this also applies to assent forms.
- Subject identification code list, screening log (if applicable), and enrollment log

  Note: European Union legislation requires this list is maintained for a minimum of 15 years after the completion or discontinuation of the study.
- Composition of the IRB and record of all communications between the investigator and the IRB as well as communications between the investigator and Amicus (or CRO)
- A list of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of eCRFs and documentation of corrections for all subjects
- Record of any body fluids or tissue samples retained
- All other source documents (eg, subject medical, hospital, laboratory records, etc)
- All other documents as listed in the ICH GCP E6 guidelines (ie, Essential Documents for the Conduct of a Clinical Trial)

Records are to be maintained in a safe and secure location. The records must be easily accessible when needed (eg, for an audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site personnel.

Normally, these records will be held in the investigator's archives. If investigators are unable to meet this obligation, they are to ask Amicus for permission to make alternative arrangements. Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution must be exercised before such action is taken.

Details of all record retention arrangements are to be documented. The investigator is also to notify Amicus of any changes in the archival arrangements, including, but not limited to archival of records at an offsite facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

17.4. Study and Site Closure

The end of study is defined as the date of database lock. The study must be closed at the site upon completion.

Upon completion or termination of the study, the study monitor will conduct site closure activities with the investigator or study personnel (as appropriate), in accordance with applicable regulations, GCP, and Amicus or its designee's standard operating procedures. Amicus or the investigator has the right to close any study site at any time. As much as possible, premature closure would occur after mutual consultation. Completion or premature termination of the study will be reported by Amicus to any relevant regulatory agency and by Amicus or the investigator to the IRB as required by the IRB.

18. PUBLICATION POLICY

All information concerning AT-GTX-501 as well as any matter concerning the operation of Amicus, such as clinical indications for AT-GTX-501, its composition, methods of manufacture, and other scientific data relating to it, that has been provided by Amicus and are unpublished, are confidential and remain the sole property of Amicus. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Amicus is obtained.

Amicus has full ownership of the data collected as part of the study.

By signing the clinical study protocol and the confidentiality agreement, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

Amicus will ensure that a final report on the study is prepared with study findings reported in a manner that complies with applicable reporting requirements for clinical study results. As required by local regulations or the IRB, a summary of the study will be submitted to the regulatory authorities and/or to the IRB.

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